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Synthesis of (±)-Hamigeran B, (−)-Hamigeran B, and (±)-1-*epi*-Hamigeran B: Use of Bulky Silyl Groups to Protect a Benzylic Carbon−Oxygen Bond from Hydrogenolysis

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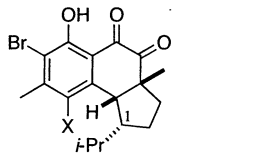
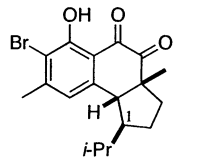
Enone **42** was converted into diene **56**, which was then subjected to hydrogenation. Use of the *tert*-butyldimethylsiloxy groups enforces facial selectivity and protects the C(5) oxygen from hydrogenolysis. The resulting product (**55**) is easily converted into hamigeran B (**1**), a marine natural product with powerful activity against herpes and polio viruses. Optically pure enone **73** was made by use of a Meyers' auxiliary and converted into (−)-hamigeran B with the natural absolute configuration.

Introduction

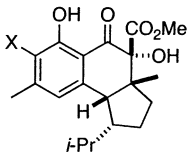
We report full details of our synthesis of hamigeran B (**1**) in both racemic[1] and optically pure[2] form, as well as a synthesis of the racemic 1-*epi*-isomer (**2**). Hamigeran B is a member of a small group of marine natural products (**1**, **3**−**9**) isolated[3] from a sponge found in shallow waters off the north eastern coast of New Zealand. Although hamigeran B is one of the structurally



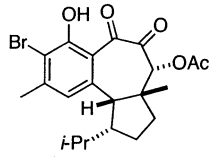
1 X = H, hamigeran B
3 X = Br, 4-bromohamigeran B



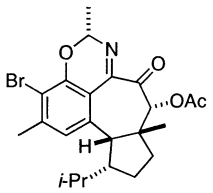
2 1-*epi*-hamigeran B



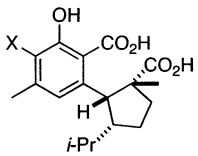
4 X = Br, hamigeran A
5 X = H, debromohamigeran A



6 hamigeran C



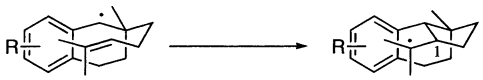
7 hamigeran D



8 X = Br, hamigeran E
9 X = H, debromohamigeran E

simpler members of this group, it would appear to be the most worthy of attention as a synthetic target because of its pronounced inhibitory activity against the polio and herpes viruses.[3] Details of the biological tests have not been published, but the compound is described[3] as showing 100% virus inhibition with only slight cytotoxicity.

SCHEME 1



10 **11**

The most obvious synthetic difficulty presented by hamigeran B is the stereochemical problem associated with the C(1) isopropyl substituent, which extends into the concave and more sterically hindered face of the structure. This orientation probably disqualifies methods that rely on stereochemical equilibration at C(1). The synthetic problems were first solved by the Nicolaou group,[4] who developed an intramolecular Diels−Alder approach that gave access not only to **1** but also to **3**, **4**, and **5**, as well as several related but unnatural stereoisomers. Our own work was aimed directly at **1**, and we were able to develop an efficient approach that could easily be adapted to produce optically pure material. Very recently, a synthesis of (−)-1-*epi*-hamigeran B was described by Mehta and Shinde.[5]

Radical Cyclization Approach. Our first approach to hamigeran B was based on the idea that radical cyclization, along the lines summarized in Scheme 1, might lead to the required stereochemistry at C(1); such a ring closure (**10** → **11**) would represent a 5-*exo*-*trigonal* pathway with the developing isopropyl group occupying an equatorial conformation. In the event, radical **10** did not behave in this way but gave instead the corresponding radical with the opposite stereochemistry at C(1).

(1) Clive, D. L. J.; Wang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3406−3409.
(2) Clive, D. L. J.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 7731−7733.
(3) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79−85.
(4) (a) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675−3678. (b) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3679−3683.
(5) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049−7053.

10.1021/jo030347v CCC: $27.50 © 2004 American Chemical Society
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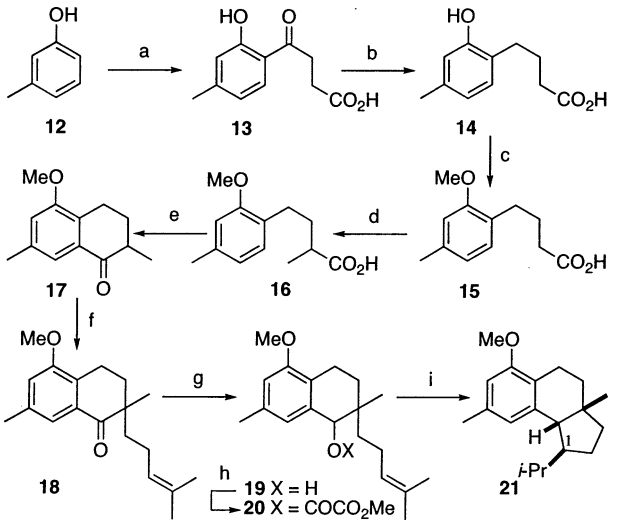
SCHEME 2[a]

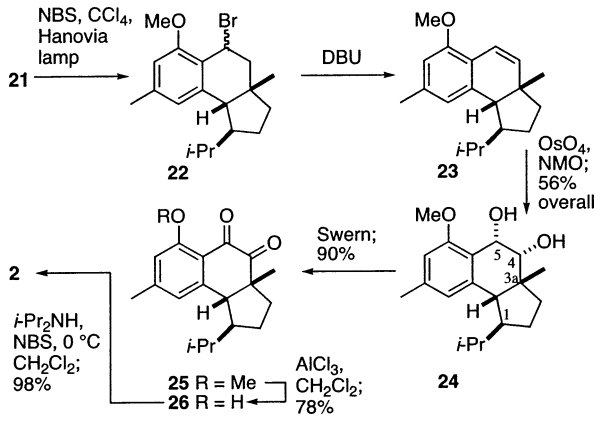


[a] Reagents and conditions: (a) succinic anhydride, $AlCl_3$; (b) Zn, $HgCl_2$, HCl, heat; (c) Me_2SO_4, NaOH, $Na_2S_2O_4$, 67% from **12**; (d) LDA, THF, HMPA, MeI, 96%; (e) $POCl_3$, $Cl_2CHCHCl_2$, heat, 83%; (f) *t*-BuOK, PhMe, 1-iodo-4-methyl-3-pentene, reflux, 80%; (g) DIBAL-H, CH_2Cl_2, 0 °C, 78%; (h) MeO_2CCOCl, CH_2Cl_2, pyridine, 93%; (i) Bu_3SnH, AIBN, PhH, reflux, 93%.

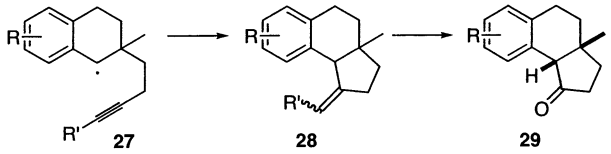
m-Cresol (**12**) was converted into keto acid **13**[6] by Friedel Crafts acylation (Scheme 2), and Clemmensen reduction[7] then gave the phenolic acid **14**.[6] O-Methylation, using Me_2SO_4 in aqueous NaOH, then afforded acid **15**[6] in 67% overall yield. The compound was easily methylated[8] α to the carboxyl group (**15** → **16**, LDA, THF, HMPA, MeI, 96%), and cyclization, by treatment with $POCl_3$ in refluxing $Cl_2CHCHCl_2$, produced the tetralone **17**.[8] This could be alklyated with 1-iodo-4-methyl-3-pentene,[9] using *t*-BuOK[10] as the base (in PhMe). Reduction of the carbonyl (DIBAL-H, 78%) gave a single alcohol (**19**), whose stereochemistry was not determined. The hydroxyl group in **19** is hindered, but it did react smoothly with MeO_2CCOCl in the presence of pyridine, giving a suitable substrate (**20**) for the intended[11] radical cyclization. Slow addition of a benzene solution of Bu_3SnH and AIBN to a refluxing solution of **20** in the same solvent produced a tricyclic compound in high yield (89%); however, it proved to be **21**, with the undesired stereochemistry at C(1), an assignment that was made at a later stage by single-crystal X-ray analysis of a derivative.

Benzylic bromination of **21** (Scheme 3) could be achieved by irradiation in the presence of NBS,[12] but the presumed products (**22**) were too unstable to allow purification. Accordingly, the material was treated directly with DBU, so as to form alkene **23**, which was obtained mixed with unchanged **21**. The latter could not be separated from

SCHEME 3

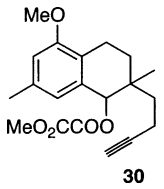


SCHEME 4



the desired product, and so the crude mixture was subjected to dihydroxylation, under standard conditions (catalytic OsO_4, stoichiometric NMO), and at this point pure **24** could be isolated (56% overall, after correction for recovered **21**). The stereochemical assignment to the hydroxyls in **24** was made on the basis of NOE measurements.[13] Swern oxidation of the diol led to the crystalline diketone **25**, whose structure was assigned by single-crystal X-ray analysis. Demethylation of **25** was effected by treatment with $AlCl_3$ (77%), and finally, bromination at 0 °C with NBS in the presence of *i*-Pr_2NH, conditions known[14] to favor *ortho* bromination, gave **2**.

At this point a cursory examination was made of radical cyclization onto a triple bond (Scheme 4, **27** → **28**). If this step were followed by ozonolysis (**28** → **29**), then the resulting ketone (**29**) might provide opportunities for introducing the isopropyl group with the correct stereochemistry by a sequence involving Grignard addition, dehydration, and hydrogenation. To this end, acetylene **30** was made by the standard methods summarized in Scheme 5. However, when **30** was treated with Bu_3SnH, hydrostannylation of the triple bond occurred. We did not investigate whether replacing the acetylenic hydrogen by a methyl group would have retarded the hydrostannylation sufficiently to allow generation of the desired radical; instead, we abandoned radical-based methods and converted ketone **31** into the tricyclic ketone **42**, by the sequence of reactions summarized in Scheme



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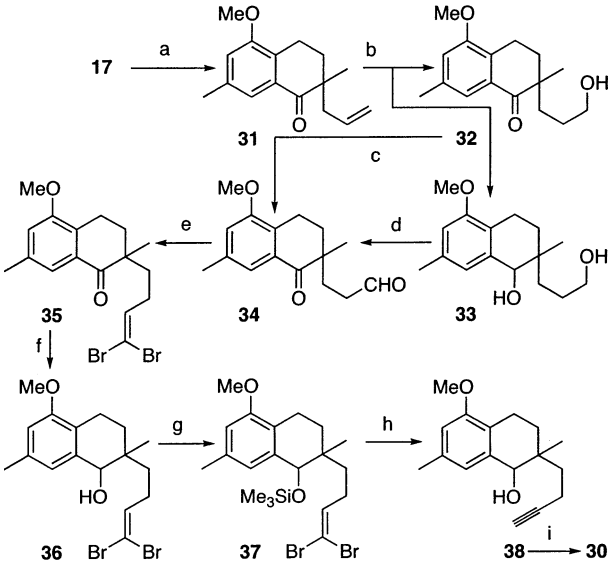
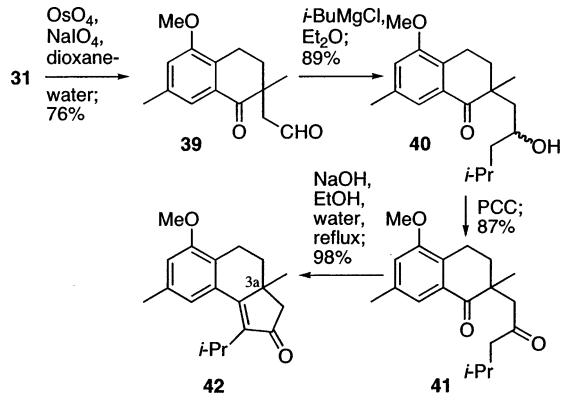
(6) Cooke, R. G.; Dowd, H. *Aust. J. Chem.* **1953**, *6*, 53−57.
(7) Martin, E. L. *J. Am. Chem. Soc.* **1936**, *58*, 1438−1442.
(8) Compare: Ruzicka, L.; Hösli, H.; Hofmann, K. *Helv. Chim. Acta* **1936**, *19*, 370−377.
(9) Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37−38.
(10) Compare: Yatabe, T.; Kayakiri, H.; Kawai, Y.; Oku, T.; Tanaka, H. *Chem. Pharm. Bull.* **1998**, *46*, 1556−1565.
(11) Compare: Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588−1589.
(12) Compare: Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592−4597.
(13) NOE between C(5)**H** and C(3a)C**H**$_3$.
(14) (a) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576−1579. (b) Krohn, K.; Bernard, S.; Flörke, U.; Hayat, N. *J. Org. Chem.* **2000**, *65*, 3218−3222.

SCHEME 5[a]



[a] Reagents and conditions: (a) LDA, THF, allyl bromide, −78 °C, 91%; (b) 9-BBN, THF, 0 °C; NaOH, H_2O_2, 20% yield of **32**, 70% yield of **33**; (c) Dess−Martin oxidation, CH_2Cl_2, 65%; (d) Swern oxidation, CH_2Cl_2, 91%; (e) CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 98%; (f) DIBAL-H, CH_2Cl_2, 0 °C, 67%; (g) Me_3SiCl, imidazole, CH_2Cl_2, 0 °C, 94%; (h) BuLi, THF, −78 °C; Bu_4NF, THF, 53%; (i) MeO_2CCOCl, CH_2Cl_2, pyridine, 80%.

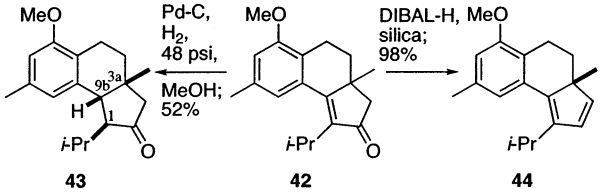
SCHEME 6



6, our hope being that the double bond in **42** could be hydrogenated with appropriate stereochemical control. We appreciated, of course, that the double bond, being tetrasubstituted, might be difficult to hydrogenate,[15] and inspection of Dreiding models exposed another potential difficulty, as it was not obvious from the shape of **42** whether hydrogenation would occur preferentially from the α or *β* face. In the event, appropriate conditions were eventually found to saturate the double bond in the desired manner.

Hydrogenation Approach. The allyl side chain of **31** was cleaved (Scheme 6) by the Lemieux−Johnson method (OsO_4, $NaIO_4$, 76%), and exposure of the resulting aldehyde (**39**) to the action of *i*-BuMgCl gave a mixture of alcohols (89%). Oxidation using PCC then afforded diketone **41** (87%). When this was boiled in aqueous ethanolic sodium hydroxide, enone **42** was produced in high yield (98%), and our efforts were now directed to the task of hydrogenating the carbon−carbon double bond from the same face as the angular methyl group at C(3a).

SCHEME 7



Hydrogenation of **42** over Pd−C (MeOH, H_2, 48 psi) generated ketone **43** as the major product (52% yield) (Scheme 7).[1] The substance is crystalline, and single-crystal X-ray analysis established the structure shown. As a working hypothesis, we assumed that the desired C(1) stereochemistry had indeed been formed but that the material had undergone epimerization, mediated by the ketone. Consequently, we sought to block this pathway by first reducing the carbonyl group. Reaction with $NaBH_4$−$CeCl_3{\cdot}7H_2O$ was very slow, but the ketone did react rapidly with DIBAL-H. However, the resulting alcohol is very acid-sensitive, and flash chromatography over silica gel gave the corresponding elimination product **44**. Hydrogenation of this compound (Pd−C, H_2, 50 psi, MeOH) did saturate the double bonds but produced an inseparable mixture of stereoisomers, with the ratio of the components varying from experiment to experiment. We attributed this stereochemical outcome to a lack of facial selectivity, and so we decided to block the α face of ketone **42** with a bulky substituent; our first method of accomplishing this task is shown in Scheme 8.

Ketone **42** was dehydrogenated with DDQ in refluxing dioxane (78%), and then dihydroxylation of the resulting alkene (**45**) under standard conditions gave the expected diol **46**. NOE measurements showed that the hydroxyl groups were *anti* to the angular methyl group, and this assignment was later confirmed by X-ray analysis of a more advanced intermediate. The hydroxyl groups were protected by ketalization (**46** → **47**, 88%) in the hope that the resulting substructure would direct subsequent hydrogenation to the opposite face.

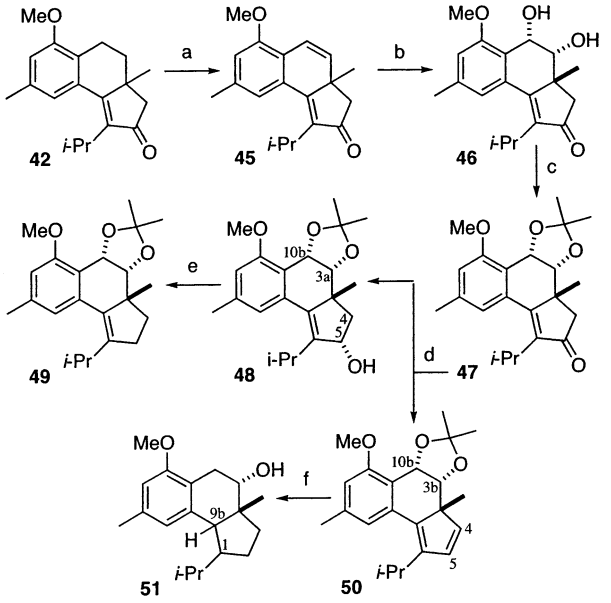
In preparation for our planned hydrogenation studies, the carbonyl group of **47** was reduced with DIBAL-H; a 2.3:1 mixture of allylic alcohol **48** (tentative stereochemistry shown at C(5)[16] and diene **50** was obtained. Hydrogenation of **48** at 33 psi for 1 h gave **49** (ca 80%), resulting from hydrogenolysis of the allylic hydroxyl, but with longer reaction times a mixture of substances lacking[17] the benzylic oxygen originally at C(10b) was also formed. Hydrogenation of diene **50**, under similar conditions but for 36 h, gave **51** [stereochemistry at C(1) and C(9b) not established] in 92% yield. Only the C(4)−C(5) double bond of **50** was reduced with Rh−Al_2O_3 (H_2, 700 psi, 50 °C, MeOH, 19 h), Wilkinson's catalyst (H_2, 400 psi, 50

(15) (a) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; Wiley: New York, 1978; p 15. (b) Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; p. 91. (c) Examples of hydrogenation of tetrasubstituted double bonds conjugated with benzene rings are known (Beilstein database); see, especially: Gray, A. C. G.; Hart, H. *J. Am. Chem. Soc.* **1968**, *90*, 2569−2578.

(16) Based on observation of NOE effects (see Supporting Information).

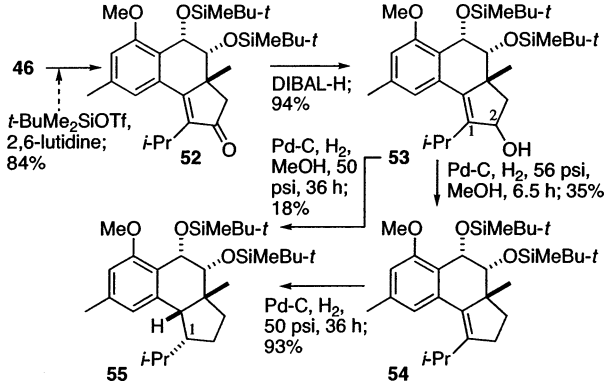
(17) As judged by the absence of ^{1}H NMR signals at ca. *δ* 5 for the benzylic C**H**-O.

SCHEME 8[a]



[a] Reagents and conditions: (a) DDQ, dioxane, reflux, 78%; (b) OsO_4, NMO, 98%; (c) $Me_2C(OMe)_2$, TsOH·pyridine, acetone, 88%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 54% yield of **48**, 23% yield of **50**; (e) Pd−C, MeOH, H_2, 30 psi, 80%; (f) Pd−C, MeOH, H_2, 35 psi, 92%.

SCHEME 9



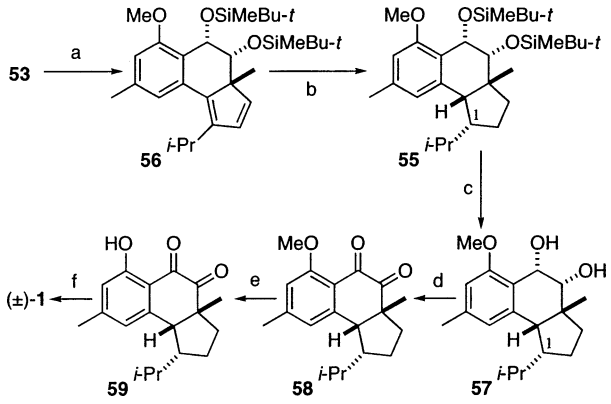
°C, MeOH, 48 h), or Raney 2800 nickel (2800 psi, 60 °C, MeOH, 67 h). Alkene **49** was inert to BH_3 or 9-BBN in refluxing THF.

Our the finding that hydrogenolysis of the C(10b) oxygen function of **50** occurred caused us to make one final modification to the route. To avoid the hydrogenolyis, we decided to protect the hydroxyl groups in **46** with substituents having sufficient bulk[18,19] to suppress coordination of the benzylic oxygen to the catalyst. To this end the hydroxyl groups were protected as *tert*-butyldimethylsilyl ethers (Scheme 9, *t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, 84%), and the resulting ketone (**52**) was reduced with DIBAL-H (94%) to alcohol **53**, whose stereochemistry at C(2) was not established. Hydrogenation of **53** for a prolonged time did indeed give the desired product (**55**), but the yield was poor (18%). With a short

(18) For studies on the mechanism of hydrogenolysis, see: Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *64*, 4172−4173.

(19) It is believed that hydrogenolysis is facilitated by development of a partial positive charge on the benzylic carbon;[18] siloxy groups have a lowered ability to stabilize an adjacent positive charge.[20]

SCHEME 10[a]



[a] Reagents and conditions: (a) MsCl, $ClCH_2CH_2Cl$, Et_3N, reflux, 80%; (b) Pd−C, H_2, 39 psi, MeOH−hexane, 36 h, 85%; (c) Bu_4NF, THF, 98%; (d) Swern oxidation, CH_2Cl_2, 92%; (e) LiCl, DMF, reflux, 78%; (f) NBS, *i*-Pr_2NH, CH_2Cl_2, 0 °C, 94%.

reaction time (6.5 h) alkene **54** was isolated (35% yield). However, prolonged hydrogenation of **54** now gave the desired **55** in excellent yield (93%). These observations suggested that the hydroxyl group of **53** has a deleterious effect on the course of the hydrogenation. Accordingly, alcohol **53** was dehydrated (Scheme 10) by mesylation conducted first at room temperature and then at reflux (in 1,2-dichloroethane). The resulting alkene (**56**) was hydrogenated as before (Pd−C, MeOH, H_2, 39 psi) to give **55** in 85% yield. Desilylation (Bu_4NF, 98%) afforded the crystalline diol **57**. At this point, X-ray analysis confirmed our stereochemical assignment, and Swern oxidation took the route as far as diketone **58**. Removal of the *O*-methyl group was initially troublesome, but we soon found that LiCl[21] in hot DMF worked well. Finally, bromination with NBS[14] in the presence of *i*-Pr_2NH gave (±)-hamigeran B, which was identified by comparison of its NMR (^1H and ^{13}C) and IR spectra with reported data.

Synthesis of (−)-Hamigeran B. Examination of our synthesis of racemic hamigeran B showed immediately that the route could be used to make optically pure material. The key asymmetric intermediate is enone **42**, and so we considered ways in which it might be prepared in enantiomerically pure form. The presence of an asymmetric quaternary carbon[22] guided us to the use of Meyers' method,[23] for which we would need lactam **65** (see Scheme 11) and iodide **69** (see Scheme 12).

γ-Butyrolactone (**60**) was converted[24] into the ester aldehyde **61** by methanolysis and oxidation (Scheme 11). Reaction with *i*-BuMgCl gave lactone **62**[25] directly, and

(20) Colvin, E. *Silicon in Organic Synthesis*, Butterworth's, London, 1981; p 12.

(21) Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis* **1987**, 287−288.

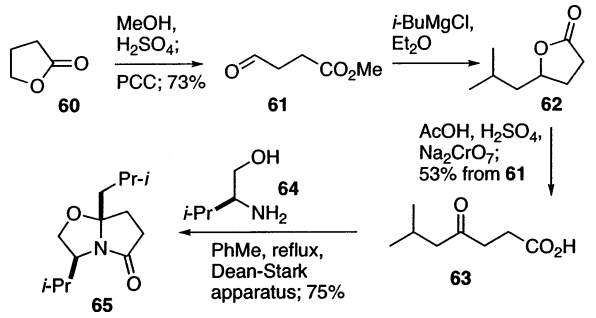
(22) Reviews on construction of quaternary centers: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419−460. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (e) See also: Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007−9071.

(23) (a) Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507−7515. (b) Sandham, D. A.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1995**, 2511−2512.

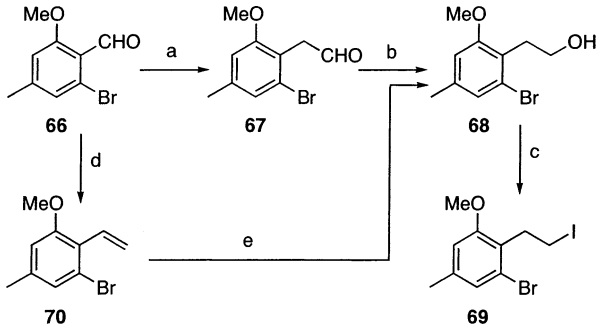
(24) Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1988**, *53*, 1064−1071.

(25) Cf. Barluenga, J.; Fernández, J. R.; Rubiera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3113−3117.

SCHEME 11



SCHEME 12[a]



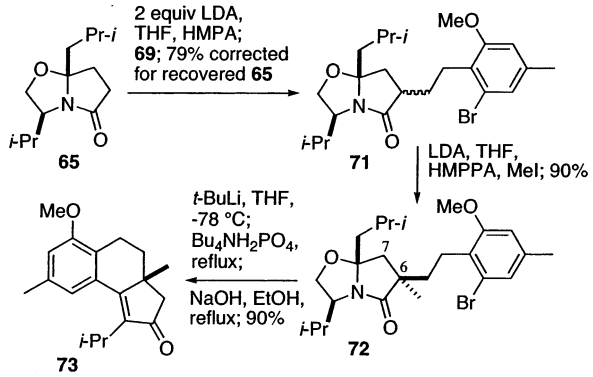
[a] Reagents and conditions: (a) $Ph_3P{=}CH(OMe)$, PhMe, 0 °C; HCl, acetone, reflux, 99%; (b) DIBAL-H, CH_2Cl_2, 0 °C, 90%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; NaI, acetone, reflux, 92%; (d) $Ph_3P{=}CH_2$, PhMe, 0 °C, 76%; (e) 9-BBN, THF, 0 °C; NaOH, H_2O_2, 87%.

oxidation under acidic conditions afforded keto acid **63**[26] in 53% overall yield from **61**. Finally, condensation with *S*-valinol[27] (**64**) under standard conditions[28] gave the required lactam **65**. In this series only the final lactam was obtained pure; the precursors were used crude.

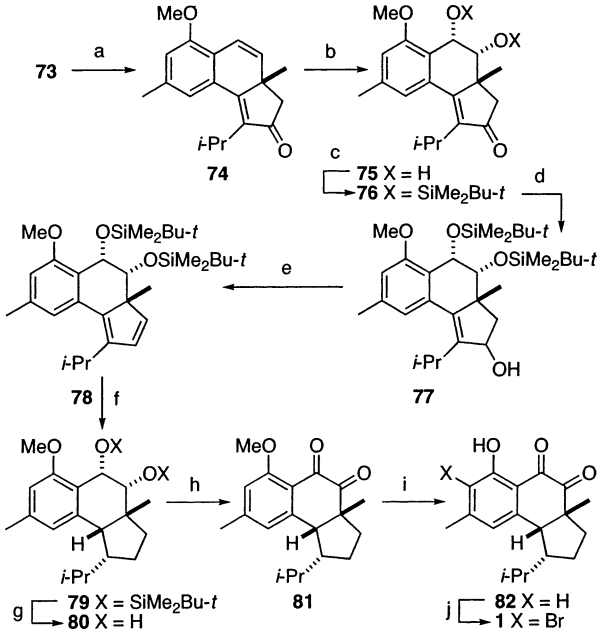
Iodide **69** was prepared from the known aldehyde **66**[29] (Scheme 12). Wittig homologation to aldehyde **67** (99%) followed by DIBAL-H reduction gave alcohol **68** (90%), and this was converted into the desired iodide by mesylation and treatment with NaI in refluxing acetone (92% overall). The intermediate alcohol **68** was also prepared by Wittig olefination of **66** (**66** → **70**, 76%) and hydroboration with 9-BBN (87%).

The two subunits **65** and **69** were joined (Scheme 13) by deprotonation of the former (1.4 equiv of LDA, THF, −78 °C) and addition of HMPA and then the iodide. The mixture was left at room temperature for 36 h, and then the coupled product **71** could be isolated in 79% [corrected for recovered lactam (30%)]. As expected,[23a] **71** was obtained as a mixture of epimers. Deprotonation (LDA, THF, −78 °C) and addition of HMPA and MeI then gave an 18:1 mixture of the desired methylated lactam **72** (90% yield) and its C(6) epimer. Treatment with *t*-BuLi at −78 °C, followed first by refluxing with an aqueous solution of $Bu_4NH_2PO_4$ (1 M) for 24 h and then with

SCHEME 13



SCHEME 14[a]



[a] Reagents and conditions: (a) DDQ, dioxane, reflux, 74%; (b) OsO_4, NMO, 81%; (c) *t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C, 73%; (d) DIBAL-H, CH_2Cl_2, 0 °C; (e) MsCl, Et_3N, $ClCH_2CH_2Cl$, 25 °C then reflux, 84% from **76**; (f) Pd−C, H_2, 39 psi, MeOH-hexane, 78%; (g) Bu_4NF, 85%; (h) Swern oxidation, CH_2Cl_2, 94%; (i) LiCl, DMF, reflux, 87%; (j) NBS, *i*-Pr_2NH, CH_2Cl_2, 0 °C, 88%.

ethanolic aqueous NaOH, brought about a cascade of reactions,[23] ultimately affording **73** in 90% overall yield. Because lactam **72**, obtained from optically pure *S*-valinol, was itself a single compound, we assumed that **73** is also optically pure, an assumption later confirmed by HPLC analysis of an advanced intermediate (**80**) on a chiral column. From this point, completion of the synthesis of (−)-hamigeran B (Scheme 14) followed the method used earlier with racemic compounds. Enone **73** was desaturated with DDQ, subjected to vicinal dihydroxylation and silylation (**73** → **74** → **75** → **76**). Again, DIBAL-H reduction and dehydration via the mesylate gave the expected diene (**76** → **77** → **78**), and the critical hydrogenation of both double bonds took the route to **79**. The silicon protecting groups were then removed in the usual way, and the resulting diol (**80**) was examined by HPLC on a chiral column. Although baseline separation of the corresponding racemic material was not possible, the trace for the optically active sample showed no sign

(26) Compare Betancourt de Perez, R. M.; Fuentes, L. M.; Larson, G. L.; Barnes, C. L.; Heeg, M. J. *J. Org. Chem.* **1986**, *51*, 2039−2043.
(27) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568−3571.
(28) Cf. Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656−1662.
(29) Made from 2,5-dimethylphenol by the method of ref 30, except that the formyl group was best generated by benzylic bromination,[31] followed by oxidation with DMSO.[32]

of a shoulder, and we judge the compound to be optically pure, as expected from the fact that it is derived from optically pure lactam **65**. Swern oxidation, demethylation with LiCl, and regioselective bromination then completed the synthesis and afforded (−)-hamigeran B with $[\alpha]_D$ −176° (*c* 0.142, CH_2Cl_2). The reported[3] specific rotation is −151.5° (*c*, 0.15, CH_2Cl_2), and so our synthesis and the earlier synthesis[4] by the Nicolaou group confirms the absolute configuration (see **1**), which had originally been assigned by analogy to that determined[33] for hamigeran A (**4**).

Conclusion

Our synthesis of hamigeran B, both racemic and optically pure material, involves very simple reactions, and this feature should make the route amenable to scale-up. Steric factors were utilized to enforce facial selectivity and to protect a benzylic carbon−oxygen bond against hydrogenolysis. Although several examples are known in which a benzylic silyl ether survives hydrogenation of di-,[34] tri-,[4a] and tetrasubstituted[35] double bonds, the reports describe such experiments without commenting on the possible role of the silicon protecting group.

Experimental Section

4-(2-Methoxy-4-methylphenyl)-2-methylbutyric Acid (16). *n*-BuLi (2.5 M in hexane, 124 mL, 0.31 mol) was added over ca. 30 min to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (45 mL, 0.32 mol) in THF (100 mL), and stirring at −78 °C was continued for 30 min. A solution of acid **15**[6] (29.1 g, 0.14 mol) in THF (100 mL) was added dropwise over ca. 30 min. Stirring was continued at −78 °C for 30 min, and at 0 °C (reaction vessel transferred to an ice bath) for another 30 min. HMPA (27 mL, 0.16 mol) was added dropwise at 0 °C. The ice bath was removed, and stirring was continued for 45 min. The mixture was cooled to 0 °C and MeI (14 mL, 0.23 mol) was added. The ice bath was removed, and stirring was continued for 3 h. The mixture was quenched with hydrochloric acid (10%, 150 mL) and extracted with Et_2O (3 × 300 mL). The combined organic extracts were washed with hydrochloric acid (10%), water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (7.5 × 40 cm), using 1:4 EtOAc−hexane containing 1% AcOH, gave acid **16**[8] (29.8 g, 96%) as a colorless oil.

5-Methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (17). $POCl_3$ (0.95 mL, 10.1 mmol) was added over ca. 2 min to a stirred and heated (135 °C) solution of acid **16** (1.87 g, 8.4 mmol) in $Cl_2CHCHCl_2$ (37 mL). The mixture was heated at 135 °C for 5 h, cooled to room temperature, quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 30 cm), using 1:32 EtOAc−hexane, gave ketone **17**[8] (1.43 g, 83%) as a pale yellow oil: FTIR (CH_2Cl_2, cast) 2931, 1684, 1611, 1282 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20 (d, J = 6.7 Hz, 3 H), 1.72−1.82 (m, 1 H), 2.12−2.18 (m, 1 H), 2.35 (s, 3 H), 2.48−2.56 (m, 1 H), 2.63−2.72 (m, 1 H), 3.00 (td, J = 4.4, 17.6 Hz, 1 H), 3.80 (s, 3 H), 6.80 (d, J = 0.9 Hz, 1 H), 7.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.3 (q), 21.4 (q), 21.9 (t), 30.7 (t), 42.1 (d), 55.6 (q), 115.1 (d), 119.0 (d), 130.3 (s), 133.1 (s), 136.6 (s), 156.7 (s), 201.2 (s); exact mass *m*/*z* calcd for $C_{13}H_{16}O_2$ 204.11504, found 204.11538.

5-Methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-3,4-dihydro-2*H*-naphthalen-1-one (18). *t*-BuOK (1.73 g, 14.67 mmol) was added in one portion to a stirred solution of ketone **17** (1.00 g, 4.89 mmol) and 5-iodo-2-methyl-2-pentene[9] (3.08 g, 14.67 mmol) in PhMe (40 mL). The resulting mixture was refluxed (oil bath at 115 °C) for 48 h, cooled, and quenched with hydrochloric acid (10%, 50 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 30 cm), using 1:32 EtOAc−hexane, gave ketone **18** [0.73 g, 80% corrected for recovered **17** (0.35 g)] as a pale yellow oil: FTIR (CH_2Cl_2, cast) 2961, 2928, 1740, 1681, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (s, 3 H), 1.45−1.53 (m, 1 H), 1.54 (s, 3 H), 1.57−1.64 (m, 1 H), 1.61 (s, 3 H), 1.84−1.92 (m, 2 H), 1.94−2.00 (m, 1 H), 2.01−2.07 (m, 1 H), 2.33 (s, 3 H), 2.80 (t, J = 6.3 Hz, 2 H), 3.83 (s, 3 H), 5.01−5.06 (m, 1 H), 6.79 (d, J = 1.1 Hz, 1 H), 7.41 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.6 (q), 18.9 (t), 21.5 (q), 21.9 (q), 22.7 (t), 25.6 (q), 33.2 (t), 36.2 (t), 44.3 (s), 55.5 (q), 114.9 (d), 119.6 (d), 124.3 (d), 129.3 (s), 131.6 (s), 132.3 (s), 136.7 (s), 156.6 (s), 202.9 (s); exact mass *m*/*z* calcd for $C_{19}H_{26}O_2$ 286.19327, found 286.19365.

5-Methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydronaphthalen-1-ol (19). DIBAL-H (1.0 M in cyclohexane, 5.0 mL, 5.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ketone **18** (0.50 g, 1.75 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 2 h at 0 °C, and $Na_2SO_4{\cdot}10H_2O$ (1.0 g) was then added. The cooling bath was removed, and stirring was continued for 30 min. The mixture was then filtered through a Celite pad (2.5 × 1 cm), using CH_2Cl_2 (20 mL) as a rinse, and the filtrate was evaporated. Flash chromatography of the residue over silica gel (2 × 25 cm), using 1:99 EtOAc−hexane, gave alcohol **19** (0.39 g, 78%) as a colorless oil: FTIR ($CDCl_3$, cast) 3424, 2928, 1613, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (s, 3 H), 1.26−1.34 (m, 1 H), 1.42−1.52 (m, 3 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 1.76−1.83 (m, 1 H), 1.97−2.12 (m, 2 H), 2.31 (s, 3 H), 2.45−2.53 (m, 1 H), 2.65 (td, J = 5.6, 12.5 Hz, 1 H), 3.80 (s, 3 H), 4.22 (s, 1 H), 5.10−5.16 (m, 1 H), 6.53 (d, J = 0.6 Hz, 1 H), 6.79 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.7 (q), 20.0 (t), 21.2 (q), 21.6 (q), 22.1 (t), 25.8 (q), 29.0 (s), 35.9 (t), 36.3 (t), 55.3 (q), 75.8 (d), 109.8 (d), 121.7 (d), 121.9 (s), 125.1 (d), 131.1 (s), 136.4 (s), 139.0 (s), 156.8 (s); exact mass *m*/*z* calcd for $C_{19}H_{28}O_2$ 288.20892, found 288.20878.

Oxalic Acid 5-Methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydronaphthalen-1-yl Methyl Ester (20). Pyridine (50 μL, 0.62 mmol), followed by MeO_2CCOCl (60 μL, 0.62 mmol), was added to a stirred solution of alcohol **19** (120 mg, 0.42 mmol) in CH_2Cl_2 (8 mL). Stirring was continued for 3 h, water (5 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:19 EtOAc−hexane, gave ester **20** (144 mg, 93%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2933, 1769, 1741, 1614, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (s, 3 H), 1.29−1.36 (m, 1 H), 1.40−1.47 (m, 1 H), 1.56−1.63 (m, 1 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.90−2.04 (m, 3 H), 2.27 (s, 3 H), 2.46−2.56 (m, 1 H), 2.78 (ddd, J = 3.0, 6.0, 18.3 Hz, 1 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 5.03−5.08 (m, 1 H), 5.80 (d, J = 0.8 Hz, 1 H), 6.60 (d, J = 0.8 Hz, 1 H), 6.76 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.5 (q), 19.7 (t), 19.9 (q), 21.4

(30) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774−2783.
(31) (a) Leed, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098−1106. (b) Mizutani, T.; Wada, K.; Kitagawa, S. *J. Org. Chem.* **2000**, *65*, 6097−6106.
(32) (a) Helms, A.; Heiler, D.; McLendon, G. *J. Am. Chem. Soc.* **1992**, *114*, 6227−6238. (b) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247−260.
(33) Cambie, R. C.; Rickard, C. E. F.; Rutledge, P. S.; Wellington, K. D. *Acta Crystallogr.* **2001**, *C57*, 958−960.
(34) (a) Connoly, T. J.; Durst, T. *Tetrahedron* **1997**, *53*, 15969−15982. (b) Mateus, C. R.; Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **2000**, *41*, 2533−3536.
(35) Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 9022−9024.

(q), 21.9 (t), 25.6 (q), 28.6 (s), 35.5 (t), 37.5 (t), 53.3 (q), 55.2 (q), 79.5 (d), 111.0 (d), 122.8 (d), 124.5 (d), 131.4 (s), 133.5 (s), 136.6 (s), 156.9 (s), 157.5 (s), 158.4 (s); exact mass *m*/*z* calcd for $C_{22}H_{30}O_5$ 374.20932, found 374.20906.

(1*R,3a*R**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene (21).** A solution of Bu_3SnH (1.8 mL, 6.69 mmol) and AIBN (50 mg, 0.3 mmol) in PhH (20 mL) was injected over ca. 15 h to a stirred and refluxing (oil bath at 85 °C) solution of ester **20** (1.01 g, 2.70 mmol) in PhH (100 mL). Stirring was continued for 3 h at 85 °C after the addition. The mixture was cooled, and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 × 25 cm), using 1:49 EtOAc−hexane, gave compound **21** (0.65 g, 89%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2950, 1612, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.98 (s, 3 H), 1.29−1.36 (m, 1 H), 1.42−1.49 (m, 2 H), 1.57−1.66 (m, 2 H), 1.70−1.79 (m, 2 H), 1.93−2.01 (m, 1 H), 2.29 (d, J = 10.2 Hz, 1 H), 2.31 (s, 3 H), 2.58−2.66 (m, 2 H), 3.79 (s, 3 H), 6.60 (d, J = 0.8 Hz, 1 H), 6.76 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.3 (q), 19.8 (t), 21.6 (q), 21.9 (t), 22.8 (q), 26.3 (q), 27.1 (d), 32.0 (t), 39.3 (t), 40.3 (s), 51.7 (d), 54.0 (d), 55.2 (q), 108.1 (d), 121.6 (s), 122.5 (d), 135.0 (s), 141.3 (s), 156.8 (s); exact mass *m*/*z* calcd for $C_{19}H_{28}O$ 272.21402, found 272.21359.

(1*R,3a*R**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene (23) via Intermediate (22).** NBS (0.42 g, 2.35 mmol) was added to a stirred solution of **21** (0.61 g, 2.24 mmol) in CCl_4 (30 mL), and the stirred solution was irradiated (standard Pyrex apparatus) with UV light (Hanovia lamp type 30620) at 10 °C for 1 h (the flask was irradiated from the top while immersed in an ice−water bath). DBU (0.5 mL, 3.27 mmol) was then added to the solution, and the mixture was stirred for 6 h. Water (20 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 25 cm), using 1:19 EtOAc−hexane, gave a colorless oil (0.59 g), which was a mixture of starting material and the desired olefin **23** (2.6:1 by ^1H NMR).

(1*R,3a*S**,4*S**,5*R**,9b*S**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-diol (24).** OsO_4 (4 mg) and NMO (0.37 g, 3.10 mmol) were added to a stirred solution of the above mixture in water (2 mL), *t*-BuOH (3 mL), CCl_4 (10 mL), and acetone (20 mL). Stirring was continued for 12 h. Water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 25 cm), using 1:9 to 1:2 EtOAc−hexane, gave diol **24** [0.11 g, 56% corrected for recovered **21** (0.43 g)] as a colorless oil: FTIR (CH_2Cl_2, cast) 3434, 2954, 1680, 1610, 1586 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 6.7 Hz, 3 H), 1.09 (s, 3 H), 1.39−1.49 (m, 2 H), 1.70−1.77 (m, 1 H), 1.91−1.98 (m, 1 H), 2.04−2.12 (m, 1 H), 2.18−2.26 (m, 1 H), 2.30 (s, 3 H), 2.47 (d, J = 9.5 Hz, 1 H), 2.75 (s, 1 H), 3.23 (s, 1 H), 3.59 (d, J = 4.1 Hz, 1 H), 3.82 (s, 3 H), 5.08 (d, J = 4.0 Hz, 1 H), 6.55 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.8 (q), 21.9 (q), 23.0 (q), 24.8 (t), 27.8 (d), 28.0 (q), 35.4 (t), 44.3 (s), 52.4 (d), 55.5 (d), 56.0 (q), 66.8 (d), 75.9 (d), 108.8 (d), 120.5 (s), 122.3 (d), 138.4 (s), 141.7 (s), 157.8 (s); exact mass *m*/*z* calcd for $C_{19}H_{28}O_3$ 304.20386, found 304.20326.

(1*R,3a*R**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione (25).** DMSO (0.20 mL, 2.80 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise over ca. 10 min to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.20 mL, 2.24 mmol) in CH_2Cl_2 (7 mL). Stirring was continued for 30 min, and diol **24** (125 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 5 min. A further portion of CH_2Cl_2 (1 mL) was used as a rinse. Stirring at −78 °C was continued for 1 h, and Et_3N (0.70 mL, 5.02 mmol) was added dropwise over ca. 2 min. Stirring was continued for 1 h, the dry ice bath was removed, and stirring was continued for 10 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:4 EtOAc−hexane, gave diketone **25** (111 mg, 90%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2957, 1723, 1678, 1605, 1566 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.75 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 1.20 (s, 3 H), 1.43−1.52 (m, 2 H), 1.56−1.63 (m, 2 H), 1.65−1.72 (m, 1 H), 2.40 (s, 3 H), 2.52−2.62 (m, 1 H), 2.67 (d, J = 11.1 Hz, 1 H), 3.90 (s, 3 H), 6.62 (s, 1 H), 6.70 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.6 (q), 21.8 (q), 22.0 (t), 22.4 (q), 22.5 (q), 27.2 (d), 33.9 (t), 55.2 (d), 56.0 (q), 56.5 (s), 57.6 (d), 111.2 (d), 118.7 (s), 122.9 (d), 147.1 (s), 147.4 (s), 161.8 (s), 179.2 (s), 200.3 (s); exact mass *m*/*z* calcd for $C_{19}H_{24}O_3$ 300.17255, found 300.17263.

(1*R,3a*R**,9b*R**)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione (26).** $AlCl_3$ (233 mg, 1.74 mmol) was added in one portion to a stirred solution of diketone **25** (105 mg, 0.35 mmol) in CH_2Cl_2 (20 mL). The mixture was refluxed (oil bath at 40 °C) for 10 h and cooled to 0 °C. Hydrochloric acid (10%, 10 mL) was added slowly and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 3:7 EtOAc−hexane (containing 1% MeOH), gave phenol **26** (77.6 mg, 77%) as a yellow oil: FTIR (CH_2Cl_2, cast) 3369, 2962, 1716, 1667, 1624, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, J = 6.2 Hz, 3 H), 1.11 (d, J = 6.1 Hz, 3 H), 1.39 (s, 3 H), 1.52−1.66 (m, 3 H), 1.71−1.78 (m, 1 H), 2.23 (ddd, J = 3.5, 5.7, 15.3 Hz, 1 H), 2.33−2.42 (m, 1 H), 2.40 (s, 3 H), 3.45 (s, 1 H), 6.64 (s, 1 H), 6.76 (s, 1 H), 8.60 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.1 (q), 20.3 (t), 21.6 (q), 22.6 (q), 23.0 (q), 28.2 (d), 35.0 (t), 46.3 (d), 52.4 (d), 63.6 (s), 115.0 (d), 117.5 (d), 119.0 (s), 150.4 (s), 157.49 (s), 157.54 (s), 204.0 (s), 206.9 (s); exact mass *m*/*z* calcd for $C_{18}H_{22}O_3$ 286.15689, found 286.15667.

(1*R,3a*R**,9b*R**)-7-Bromo-6-hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione (1-*epi*-Hamigeran B) (2).** NBS (3.0 mg, 0.017 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise over ca. 5 min to a stirred and cooled (0 °C) solution of phenol **26** (4.0 mg, 0.014 mmol) and *i*-Pr_2NH (ca 0.01 mL, 0.07 mmol) in CH_2Cl_2 (2 mL). The cold bath was removed after the addition, and stirring was continued for 3.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 30 cm), using 1:3 EtOAc−hexane (containing 1%v/v MeOH), gave 1-*epi*-hamigeran B (**2**) (5.0 mg, 98%) as a yellow oil: FTIR (CH_2Cl_2, cast) 3326, 2962, 1717, 1669, 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, J = 6.1 Hz, 3 H), 1.10 (d, J = 6.1 Hz, 3 H), 1.39 (s, 3 H), 1.51−1.65 (m, 3 H), 1.72−1.79 (m, 1 H), 2.22 (ddd, J = 3.6, 5.7, 15.1 Hz, 1 H), 2.35−2.44 (m, 1 H), 2.51 (s, 3 H), 3.43 (s, 1 H), 6.90 (s, 1 H), 9.20 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.0 (q), 20.3 (t), 21.6 (q), 23.0 (q), 24.5 (q), 28.2 (d), 35.1 (t), 46.2 (d), 52.2 (d), 63.7 (s), 110.0 (s), 118.7 (d), 119.6 (s), 149.2 (s), 154.2 (s), 155.6 (s), 203.7 (s), 206.2 (s); exact mass *m*/*z* calcd for $C_{18}H_{21}{}^{79}BrO_3$ 364.06741, found 364.06764.

2-Allyl-5-methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (31). *n*-BuLi (2.5M, 2.4 mL, 6.0 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (0.93 mL, 6.6 mmol) in THF (20 mL), and stirring at −78 °C was continued for 30 min. A solution of ketone **17** (1.09 g, 5.3 mmol) in THF (10 mL) was added dropwise over ca. 15 min, and stirring was continued at −78 °C for 1.5 h. Allyl bromide (0.93 mL, 10.5 mmol) was added dropwise and stirring at −78 °C was continued for 2 h. The cooling bath was removed, and stirring was continued for 10 h. The mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic

extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 30 cm), using 1:32 EtOAc−hexane, gave ketone **31** (1.18 g, 91%) as a yellow oil: FTIR (CH_2Cl_2, cast) 3074, 2930, 1682, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (s, 3 H), 1.80−1.88 (m, 1 H), 1.97−2.03 (m, 1 H), 2.24 (tdd, J = 1.1, 7.5, 13.7 Hz, 1 H), 2.34 (s, 3 H), 2.40 (dd, J = 7.3, 13.8 Hz, 1 H), 2.74−2.88 (m, 2 H), 3.80 (s, 3 H), 5.00−5.07 (m, 2 H), 5.73−5.81 (m, 1 H), 6.80 (d, J = 1.0 Hz, 1 H), 7.45 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.8 (t), 21.5 (q), 21.7 (q), 32.8 (t), 40.9 (t), 44.2 (s), 55.6 (q), 115.0 (d), 118.0 (t), 119.6 (d), 129.4 (s), 132.1 (s), 134.1 (d), 136.7 (s), 156.6 (s), 202.5 (s); exact mass m/z calcd for $C_{16}H_{20}O_2$ 244.14633, found 244.14654.

(5-Methoxy-2,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetaldehyde (39). OsO_4 (4 mg) was added to a solution of **31** (78 mg, 0.32 mmol) in dioxane−water (3:1, 10 mL). The mixture was stirred for 30 min, and $NaIO_4$ (0.21 g, 1.00 mmol) was added. Stirring was continued for 3.5 h. Water (10 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:19 EtOAc−hexane, gave aldehyde **39** (60 mg, 76%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2935, 2841, 2736, 1719, 1679, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 3 H), 1.92 (td, J = 4.7, 13.4 Hz, 1 H), 2.15−2.22 (m, 1 H), 2.35 (s, 3 H), 2.53 (dd, J = 2.5, 16.1 Hz, 1 H), 2.73−2.82 (m, 2 H), 2.94 (td, J = 4.7, 18.2 Hz, 1 H), 3.85 (s, 3 H), 6.81 (s, 1 H), 7.43 (s, 1 H), 9.82 (t, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.8 (t), 21.5 (q), 21.7 (q), 33.6 (t), 43.8 (t), 51.3 (s), 55.6 (q), 115.5 (d), 119.7 (d), 129.1 (s), 131.5 (s), 137.1 (s), 156.6 (s), 201.2 (s), 201.3 (d); exact mass m/z calcd for $C_{15}H_{18}O_3$ 246.12560, found 246.12556.

2-(2-Hydroxy-4-methylpentyl)-5-methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (40). *i*-BuMgCl (2.0 M, 3.0 mL, 6.0 mmol) was added dropwise over ca. 10 min to a stirred and cooled (−78 °C) solution of aldehyde **39** (1.36 g, 5.5 mmol) in Et_2O (60 mL). The mixture was stirred at −78 °C for 1 h. The cooling bath was left in place but not recharged, and stirring was continued for 10 h. The mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 25 cm), using 1:19 EtOAc−hexane, gave the intermediate alcohols **40** (1.49 g, 89%) as a yellow oil: FTIR (CH_2Cl_2, cast) 3443, 2954, 1676, 1608 cm^{-1}; exact mass m/z calcd for $C_{19}H_{28}O_3$ 304.20386, found 304.20346. Both the ^1H and ^{13}C NMR spectra indicated the presence of two alcohols (ca 1:1).

5-Methoxy-2,7-dimethyl-2-(4-methyl-2-oxopentyl)-3,4-dihydro-2*H*-naphthalen-1-one (41). PCC (1.9 g, 8.6 mmol) was added to a stirred solution of the above alcohols in CH_2Cl_2 (60 mL). The mixture was stirred at room temperature for 3.5 h and then filtered through a Celite pad (2.5 × 3 cm). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 30 cm), using 1:9 EtOAc−hexane, gave diketone **41** (1.32 g, 79% over two steps) as a yellow oil: FTIR (CH_2Cl_2, cast) 2957, 1712, 1681, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, J = 6.6 Hz, 6 H), 1.22 (s, 3 H), 1.84 (ddd, J = 3.7, 5.2, 13.4 Hz, 1 H), 2.12 (septet, J = 6.6 Hz, 1 H), 2.28 (dd, J = 3.0, 6.9 Hz, 2 H), 2.37 (s, 3 H), 2.40−2.48 (m, 1 H), 2.68−2.78 (m, 1 H), 2.81 (AB q, J = 17.3 Hz, $\Delta\nu_{AB}$ = 217.4 Hz, 2 H), 2.97 (td, J = 4.5, 17.9 Hz, 1 H), 3.85 (s, 3 H), 6.84 (d, J = 1.2 Hz, 1 H), 7.50 (d, J = 0.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.8 (t), 21.6 (q), 22.2 (q), 22.7 (q), 24.8 (d), 32.5 (t), 43.5 (t), 51.3 (s), 52.7 (t), 55.7 (q), 115.2 (d), 119.7 (d), 129.1 (s), 131.9 (s), 136.7 (s), 156.5 (s), 201.5 (s), 208.5 (s); exact mass m/z calcd for $C_{19}H_{26}O_3$ 302.18820, found 302.18811.

1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one (42). NaOH (50%, 5 mL) was added to a stirred solution of diketone **41** (0.28 g, 0.93 mmol) in EtOH (15 mL). The mixture was refluxed (oil bath at 80 °C) for 36 h, cooled to room temperature, neutralized with hydrochloric acid (3%, 20 mL), and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 25 cm), using 1:9 EtOAc−hexane, gave enone **42** (0.26 g, 98%) as yellow plates: mp 105−106 °C; FTIR (CH_2Cl_2, cast) 2956, 1693, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 3 H), 1.19 (d, J = 6.9 Hz, 3 H), 1.37 (d, J = 7.0 Hz, 3 H), 1.66−1.74 (m, 1 H), 2.07 (ddd, J = 1.0, 6.9, 13.2 Hz, 1 H), 2.26 (AB q, J = 18.5 Hz, $\Delta\nu_{AB}$ = 60.8 Hz, 2 H), 2.37 (s, 3 H), 2.61−2.71 (m, 1 H), 2.86 (dd, J = 7.0, 18.8 Hz, 1 H), 3.12 (septet, J = 7.0 Hz, 1 H), 3.83 (s, 3 H), 6.70 (s, 1 H), 6.86 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.8 (q), 20.6 (q), 20.8 (t), 21.7 (q), 23.0 (q), 25.7 (d), 36.0 (t), 38.7 (t), 51.1 (s), 55.3 (q), 111.8 (d), 120.9 (d), 123.5 (s), 131.5 (s), 136.0 (s), 140.6 (s), 157.2 (s), 170.1 (s), 208.2 (s); exact mass m/z calcd for $C_{19}H_{24}O_2$ 284.17764, found 284.17741.

(1*R,3a*S**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-1,3,3a,4,5,9b-hexahydrocyclopenta[*a*]naphthalene-2-one (43).** Pd−C (10%, 10 mg) was added to a solution of enone **42** (17.8 mg, 0.06 mmol) in MeOH (1 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (48 psi) for 9 h. The mixture was filtered through a Celite pad (1 × 2.5 cm), using CH_2Cl_2 (5 mL) as a rinse, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using hexane, gave ketone **43** (9.3 mg, 52%, major product) as white crystals: mp 98−99 °C; FTIR (CH_2Cl_2, cast) 2956, 1735, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.0 (d, J = 6.9 Hz, 3 H), 1.09 (s, 3 H), 1.16 (d, J = 7.0 Hz, 3 H), 1.50−1.62 (m, 2 H), 2.06−2.24 (m, 4 H), 2.32 (s, 3 H), 2.46−2.55 (m, 1 H), 2.76 (d, J = 10.6 Hz, 1 H), 2.78−2.85 (m, 1 H), 3.80 (s, 3 H), 6.52 (s, 1 H), 6.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 16.8 (q), 19.8 (t), 21.6 (q), 21.8 (q), 23.6 (q), 27.8 (d), 30.0 (t), 34.8 (s), 48.9 (d), 55.2 (q), 55.9 (t), 61.1 (d), 108.8 (d), 120.1 (s), 122.5 (d), 135.7 (s), 138.0 (s), 157.3 (s), 219.5 (s); exact mass m/z calcd for $C_{19}H_{26}O_2$ 286.19327, found 286.19342.

1-Isopropyl-6-methoxy-3a,8-dimethyl-4,5-dihydro-3a*H*-cyclopenta[*a*]naphthalene (44). DIBAL-H (1 M in cyclohexane, 0.4 mL, 0.4 mmol) was added dropwise to a stirred and cooled (0 °C) solution of enone **42** (76 mg, 0.27 mmol) in CH_2Cl_2 (5 mL). After the addition, the ice bath was removed, and stirring was continued for 5 h. The mixture was recooled to 0 °C, $Na_2SO_4 \cdot 10H_2O$ (0.5 g) was added, and stirring was continued for 30 min. The mixture was filtered through a Celite pad (1 × 1.5 cm), using CH_2Cl_2 as a rinse. The solvent was evaporated, and the residue was dissolved in $CDCl_3$ (2 mL) and stirred for 3 h [this step was carried out because in a previous experiment conversion of the initial alcohol to the diene was observed after leaving an NMR sample overnight in $CDCl_3$]. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm), using 1:9 EtOAc−hexane, gave diene **44** (71 mg, 98%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3057, 2959, 1696, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (s, 3 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.28 (d, J = 6.9 Hz, 3 H), 1.22−1.30 (m, 1 H), 2.12 (ddd, J = 0.8, 6.5, 11.9 Hz, 1 H), 2.36 (s, 3 H), 2.58−2.67 (m, 1 H), 2.86 (dd, J = 6.7, 18.2 Hz, 1 H), 3.20 (septet, J = 6.8 Hz, 1 H), 3.80 (s, 3 H), 6.37 (d, J = 5.3 Hz, 1 H), 6.46 (d, J = 5.3 Hz, 1 H), 6.55 (s, 1 H), 6.83 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.3 (q), 21.1 (t), 21.8 (q), 22.0 (q), 22.9 (q), 26.2 (d), 31.7 (t), 52.3 (s), 55.2 (q), 108.7 (d), 119.3 (d), 121.6 (s), 129.1 (d), 133.7 (s), 135.5 (s), 142.8 (s), 143.1 (s), 145.5 (d), 157.2 (s); exact mass m/z calcd for $C_{19}H_{24}O$ 268.18271, found 268.18297.

(2*R,3a*S**,4*S**,5*R**)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*a*]naphthalene-2-ol (53).** DIBAL-H (1 M in cyclohexane, 4.0 mL, 4.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of enone **52** (0.88 g, 1.6 mmol) in CH_2Cl_2 (50 mL). After the addition, the ice bath was removed, and stirring was continued for 10 h. The mixture was recooled to 0 °C, $Na_2SO_4 \cdot 10H_2O$ (1.5 g) was added, and

stirring was continued for 30 min. The mixture was filtered through a Celite pad (1 × 2.5 cm), using CH_2Cl_2 as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 25 cm), using 1:19 EtOAc−hexane, gave alcohol **53** (0.83 g, 94%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3604, 2955, 1609 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ −0.14 (s, 3 H), 0.04 (s, 3 H), 0.20 (s, 3 H), 0.34 (s, 3 H), 0.98 (s, 1 H), 1.00 (s, 3 H), 1.02 (s, 9 H), 1.07 (s, 9 H), 1.36 (d, J = 7.1 Hz, 3 H), 1.40 (d, J = 7.0 Hz, 3 H), 2.14 (s, 3 H), 2.23 (dd, J = 6.0, 11.7 Hz, 1 H), 2.55 (dd, J = 8.5, 11.7 Hz, 1 H), 3.35 (s, 3 H), 3.45 (d, J = 2.9 Hz, 1 H), 3.48 (septet, J = 7.0 Hz, 1 H), 5.10−5.18 (m, 1 H), 5.40 (d, J = 2.9 Hz, 1 H), 6.38 (s, 1 H), 6.95 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ −5.2 (q), −4.7 (q), −4.3 (q), −3.6 (q), 18.50 (s), 18.52 (s), 20.5 (q), 21.9 (q), 23.l (q), 26.3 (q), 26.4 (q), 26.6 (q), 28.7 (d), 46.7 (t), 48.1 (s), 54.9 (q), 68.2 (d), 78.2 (d), 80.0 (d), 110.0 (d), 120.9 (d), 125.1 (s), 136.5 (s), 138.7 (s), 141.4 (s), 142.8 (s), 156.2 (s); exact mass m/z calcd for $C_{31}H_{52}O_3Si_2$ [M − H_2O] 528.34552, found 528.34401.

(3*S*,7a*S*)-7a-Isobutyl-3-isopropyltetrahydropyrrolo-[2,1-*b*]oxazol-5-one (65). *S*-Valinol was prepared by the literature method and had $[\alpha]^{25}_D$ = +17.4° (*c* 10, EtOH) [lit.[27] $[\alpha]^{25}_D$ = +17° (*c* 10, EtOH)]. Acid **63** (4.2 g, 26.5 mmol) was added to a stirred solution of *S*-valinol (2.7 g, 26.5 mmol) in PhMe (150 mL) and the solution was refluxed for 15 h, using a Dean−Stark trap. The mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (5 × 30 cm), using 1:19 *t*-BuOMe−CH_2Cl_2, gave lactam **65** (4.5 g, 75%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2957, 2871, 1715 cm^{-1}; $[\alpha]_D$ = +80.5° (*c* 1.22, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.83 (d, J = 6.7 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 1.02 (d, J = 6.7 Hz, 3 H), 1.52 (dd, J = 5.6, 14.2 Hz, 1 H), 1.56−1.63 (m, 1 H), 1.65 (dd, J = 7.0, 14.3 Hz, 1 H), 1.77 (septet, J = 6.6 Hz, 1 H), 2.03 (td, J = 9.9, 13.5 Hz, 1 H), 2.23−2.30 (m, 1 H), 2.44 (ddd, J = 2.7, 10.4, 17.2 Hz, 1 H), 2.66 (td, J = 9.8, 17.2 Hz, 1 H), 3.54 (td, J = 7.3, 11.6 Hz, 1 H), 3.72 (dd, J = 8.8, 6.9 Hz, 1 H), 4.15 (dd, J = 7.7, 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.9 (q), 20.8 (q), 23.7 (q), 24.2 (q), 24.8 (d), 31.2 (t), 33.0 (t), 34.1 (d), 61.7 (d), 71.0 (t), 102.3 (s), 179.3 (s); exact mass m/z calcd for $C_{13}H_{23}O_2$ 225.17288, found 225.17213.

2-Bromo-6-methoxy-4-methylphenylacetaldehyde (67). $(Me_3Si)_2NK$ (0.5 M in PhMe, 26.0 mL, 13.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $MeOCH_2P(Ph_3)Cl$ (5.3 g, 15.0 mmol) in PhMe (80 mL). The ice bath was removed, and stirring was continued for 1 h. Aldehyde **66**[29] (2.29 g, 10.0 mmol) in PhMe (20 mL) was added dropwise, and the mixture was then stirred at room temperature for 2 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Dilute hydrochloric acid (3 N, 50 mL) and acetone (100 mL) were added to the residue, and the mixture was refluxed for 3.5 h, cooled, and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 30 cm), using 1:19 EtOAc−hexane, gave aldehyde **67** (4.6 g, 99%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3003, 2961, 2842, 2735, 1714, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 3.78 (s, 3 H), 3.83 (d, J = 1.6 Hz, 2 H), 6.62 (s, 1 H), 7.03 (d, J = 0.7 Hz, 1 H), 9.62 (t, J = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.3 (q), 44.3 (t), 55.8 (q), 110.5 (d), 118.9 (s), 125.3 (d), 125.7 (s), 139.8 (s), 158.3 (s), 199.1 (s); exact mass m/z calcd for $C_{10}H_{11}{}^{79}BrO_2$ 241.99425, found 241.99383.

2-(2-Bromo-6-methoxy-4-methylphenyl)ethanol (68). DIBAL-H (1.0 M in cyclohexane, 25.0 mL, 25.0 mmol) was added dropwise over ca. 5 min to a stirred and cooled (0 °C) solution of aldehyde **67** (4.8 g, 19.7 mmol) in CH_2Cl_2 (100 mL). The ice bath was removed, and stirring was continued for 30 min. The mixture was recooled to 0 °C, $Na_2SO_4{\cdot}10H_2O$ (5 g) was added, and stirring was continued for 1 h. The mixture was filtered through a Celite pad, using CH_2Cl_2 as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 30 cm), using 1:4 EtOAc−hexane, gave alcohol **68** (4.3 g, 90%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3299, 2940, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 1 H), 2.28 (s, 3 H), 3.08 (t, J = 6.8 Hz, 2 H), 3.76 (t, J = 6.8 Hz, 2 H), 3.78 (s, 3 H), 6.60 (s, 1 H), 6.99 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.1 (q), 32.9 (t), 55.8 (q), 61.9 (t), 110.6 (d), 123.8 (s), 125.4 (d), 125.5 (s), 138.5 (s), 158.2 (s); exact mass m/z calcd for $C_{10}H_{13}{}^{81}BrO_2$ 246.00784, found 246.00758.

1-Bromo-2-(2-iodoethyl)-3-methoxy-5-methylbenzene (69). Et_3N (3.8 mL, 27.3 mmol) was added to a stirred and cooled (0 °C) solution of alcohol **68** (4.47 g, 18.2 mmol) in CH_2Cl_2 (50 mL), and then MsCl (1.6 mL, 20.9 mmol) was added dropwise. The cold bath was removed, stirring was continued for 2 h, and the mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in acetone (80 mL), and dry NaI (11.0 g, 73.4 mmol) was added. The resulting mixture was refluxed for 24 h and then cooled. Water (60 mL) was added, and the mixture was extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 × 30 cm), using 1:19 EtOAc−hexane, gave **69** (5.9 g, 92%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2920, 1604 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.86 (s, 3 H), 3.08 (s, 3 H), 3.14−3.18 (m, 2 H), 3.43 (t, J = 8.4 Hz, 2 H), 6.12 (s, 1 H), 6.85 (d, J = 0.6 Hz, 1 H); ^{13}C NMR (C_6D_6, 125.7 MHz) δ 1.7 (t), 21.0 (q), 34.8 (t), 55.2 (q), 110.8 (d), 125.3 (s), 125.8 (d), 126.8 (s), 139.1 (s), 158.2 (s); exact mass m/z calcd for $C_{10}H_{12}{}^{79}BrIO$ 353.91162, found 353.91199.

1-Bromo-3-methoxy-5-methyl-2-vinylbenzene (70). $(Me_3Si)_2NK$ (0.5 M in PhMe, 76.0 mL, 38.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of Ph_3PCH_3Br (15.5 g, 42.5 mmol) in PhMe (40 mL). The ice bath was removed, and stirring was continued for 1 h. The solution was recooled to 0 °C, and a solution of aldehyde **66**[29] (7.3 g, 31.9 mmol) in PhMe (20 mL) was added dropwise over ca. 5 min. The ice bath was removed, and stirring was continued for 10 h. The mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 30 cm), using 1:19 EtOAc−hexane, gave olefin **70** (5.5 g, 76%) as colorless oil: FTIR (CH_2Cl_2, cast) 2935, 1620, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3 H), 3.81 (s, 3 H), 5.50 (dd, J = 2.1, 11.8 Hz, 1 H), 5.91 (dd, J = 2.1 Hz, 17.7 Hz, 1 H), 6.64 (s, 1 H), 6.78 (dd, J = 7.9, 13.8 Hz, 1 H), 7.04 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.2 (q), 55.7 (q), 111.1 (d), 120.4 (t), 123.5 (s), 124.6 (s), 125.8 (d), 131.9 (d), 138.9 (s), 158.3 (s); exact mass m/z calcd for $C_{10}H_{11}{}^{81}BrO$ 227.99728, found 227.99723.

2-(2-Bromo-6-methoxy-4-methylphenyl)ethanol (68) from (70). 9-BBN (0.5 M in THF, 58 mL, 29 mmol) was added dropwise over 20 min to a stirred and cooled (0 °C) solution of olefin **70** (5.48 g, 24.1 mmol) in THF (100 mL). The ice bath was removed, and stirring was continued for 10 h. The mixture was cooled to 0 °C and quenched by dropwise addition of MeOH (40 mL). Aqueous NaOH (2 M, 100 mL) and 30% H_2O_2 (20 mL) were poured into the stirred mixture. Stirring was continued for 2 h, and the mixture was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave alcohol **68** (4.27 g, 87%), identical to material made from **67**.

(3*S*,7a*R*)-6-[2-(2-Bromo-6-methoxy-4-methylphenyl)-ethyl]-7a-isobutyl-3-isopropyltetrahydropyrrolo[2,1-*b*]-oxazol-5-one (71). BuLi (2.5 M in hexanes, 6.5 mL, 16.25 mmol) was added dropwise over ca. 5 min to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (2.4 mL, 17.12 mmol) in

THF (80 mL). Stirring was continued for 30 min at −78 °C, and a solution of lactam **65** (2.43 g, 10.80 mmol) in THF (20 mL) was added dropwise over ca. 15 min. Stirring at −78 °C was continued for 1 h, and HMPA (2.2 mL, 12.64 mmol) was added dropwise, followed by iodide **69** (6.27 g, 17.64 mmol). The resulting mixture was stirred at −78 °C for 1 h, the cold bath was removed, and stirring was continued for 36 h. The mixture was then quenched with saturated aqueous NH_4Cl (80 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 35 cm), using 1:9 EtOAc−hexane, gave the monoalkylated lactam **71** as a mixture of two diastereoisomers [2.7 g, 79% yield, corrected for recovered **65** (730 mg, 30% recovery)]. We did not separate the isomers at this stage; however, a pure sample of the major isomer was obtained from one of the flash chromatography fractions: FTIR (CH_2Cl_2, cast) 2956, 1711, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 1.01 (d, J = 6.7 Hz, 3 H), 1.40−1.84 (m, 6 H), 2.08−2.18 (m, 1 H), 2.26 (s, 3 H), 2.60 (dd, J = 8.6, 12.8 Hz, 1 H), 2.72−2.84 (m, 3 H), 3.52−3.58 (m, 1 H), 3.72−3.80 (m, 1 H), 3.76 (s, 3 H), 4.18 (dd, J = 8.7, 9.6 Hz, 1 H), 6.56 (s, 1 H), 6.94 (t, J = 0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.0 (q), 20.8 (q), 21.1 (q), 23.9 (q), 24.2 (q), 24.9 (d), 27.3 (t), 29.9 (t), 34.2 (d), 39.6 (t), 44.2 (d), 45.0 (t), 55.6 (q), 61.1 (d), 71.0 (t), 99.9 (s), 110.4 (d), 125.06 (s), 125.09 (d), 126.9 (s), 137.9 (s), 158.0 (s), 179.7 (s); exact mass m/z calcd for $C_{23}H_{34}{}^{81}BrNO_3$ 453.17017, found 453.16963.

(3*S*,6*R*,7a*R*)-6-[2-(2-Bromo-6-methoxy-4-methylphenyl)ethyl]-7a-isobutyl-3-isopropyl-6-methyltetrahydropyrrolo-[2,1-*b*]oxazol-5-one] (72). *n*-BuLi (2.5 M, 3.5 mL, 8.75 mmol) was added dropwise over ca. 5 min to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (1.3 mL, 9.27 mmol) in THF (40 mL), and stirring at −78 °C was continued for 30 min. A solution of lactam **71** (2.25 g, 5.00 mmol) in THF (10 mL) was added dropwise over ca. 15 min, and stirring at −78 °C was continued for 1.5 h. HMPA (1.2 mL, 6.90 mmol) was added dropwise over ca. 5 min, followed by MeI (1.2 mL, 19.00 mmol), which was also added over ca. 5 min. Stirring at −78 °C was continued for 1 h, the cooling bath was removed, and stirring was continued for 12 h. The mixture was quenched with aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 35 cm), using 1:19 *t*-BuOMe-hexane, gave the dialkylated lactam **72** (2.1 g, 90%) together with the *exo* isomer (0.1 g, 5%). Lactam **72**: FTIR (CH_2Cl_2, cast) 2956, 1711, 1604 cm^{-1}; $[\alpha]_D$ = +18.6° (*c* 0.500, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 1.24 (s, 3 H), 1.51−1.90 (m, 6 H), 2.20 (AB q, J = 13.9 Hz, $\Delta\nu_{AB}$ = 223.6 Hz, 2 H), 2.23 (s, 3 H), 2.70−2.83 (m, 2 H), 3.53−3.67 (m, 2 H), 3.76 (s, 3 H), 4.18 (t, J = 7.9 Hz, 1 H), 6.56 (s, 1 H), 6.95 (t, J = 0.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.0 (q), 20.9 (q), 21.1 (q), 23.4 (q), 23.6 (q), 24.2 (q), 24.9 (d), 25.0 (t), 34.5 (d), 38.1 (t), 43.6 (t), 45.2 (t), 47.4 (s), 55.7 (q), 62.1 (d), 70.3 (t), 99.1 (s), 110.4 (d), 124.8 (s), 125.0 (d), 126.9 (s), 137.9 (s), 157.8 (s), 184.3 (s); exact mass m/z calcd for $C_{24}H_{36}{}^{81}BrNO_3$ 467.18583, found 467.18614.

(3a*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one (73). *t*-BuLi (1.7 M, 7.0 mL, 11.9 mmol) was added dropwise over ca. 15 min to a stirred and cooled (−78 °C) solution of lactam **72** (2.1 g, 4.5 mmol) in THF (30 mL). Stirring at −78 °C was continued for 1.75 h, and the mixture was then quenched with aqueous *n*-$Bu_4NH_2PO_4$ (1 M, 50 mL). The THF was evaporated at room temperature (rotary evaporator), and the aqueous solution was refluxed for 24 h. The mixture was cooled and extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated.

The residue was dissolved in EtOH (20 mL), and aqueous NaOH (5 N, 15 mL) was added. The mixture was refluxed for 24 h, cooled to room temperature, and extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 25 cm), using 1:9 EtOAc−hexane, gave enone **73** (1.15 g, 90%) as a yellow oil: FTIR ($CHCl_3$, cast) 2957, 1693, 1610 cm^{-1}; $[\alpha]_D$ = − 345.1° (*c* 0.304, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 3 H), 1.19 (d, J = 6.9 Hz, 3 H), 1.37 (d, J = 7.0 Hz, 3 H), 1.66−1.74 (m, 1 H), 2.07 (ddd, J = 1.0, 6.9, 13.2 Hz, 1 H), 2.26 (AB q, J = 18.5 Hz, $\Delta\nu_{AB}$ = 48.9 Hz, 2 H), 2.37 (s, 3 H), 2.61−2.71 (m, 1 H), 2.86 (dd, J = 7.0, 18.8 Hz, 1 H), 3.12 (septet, J = 7.0 Hz, 1 H), 3.83 (s, 3 H), 6.70 (s, 1 H), 6.86 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8 (q), 20.6 (q), 20.8 (t), 21.7 (q), 23.0 (q), 25.7 (d), 36.0 (t), 38.7 (t), 51.1 (s), 55.3 (q), 111.8 (d), 120.9 (d), 123.5 (s), 131.5 (s), 136.0 (s), 140.6 (s), 157.2 (s), 170.1 (s), 208.2 (s); exact mass m/z calcd for $C_{19}H_{24}O_2$ 284.17764, found 284.17735.

(3a*S*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a-dihydrocyclopenta[*a*]naphthalen-2-one (74). DDQ (1.36 g, 6.0 mmol) was added in one lot to a stirred solution of enone **73** (1.15 g, 4.0 mmol) in 1,4-dioxane (60 mL), and the mixture was refluxed for 10 h (Ar atmosphere), cooled to room temperature, and filtered through a pad of flash chromatography silica gel (5 × 3.5 cm), using Et_2O (100 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 30 cm), using 1:9 EtOAc−hexane, gave ketone **74** (0.83 g, 74%) as a yellow oil: FTIR ($CHCl_3$, cast) 2958, 1696, 1603 cm^{-1}; $[\alpha]_D$ = −786.9° (*c* 0.352, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 6.8 Hz, 3 H), 1.18 (s, 3 H), 1.36 (d, J = 7.1 Hz, 3 H), 2.40 (s, 3 H), 2.44 (AB q, J = 17.6 Hz, $\Delta\nu_{AB}$ = 108.8 Hz, 2 H), 3.02 (septet, J = 7.0 Hz, 1 H), 3.80 (s, 3 H), 6.05 (d, J = 9.6 Hz, 1 H), 6.72 (d, J = 9.5 Hz, 1 H), 6.73 (s, 1 H), 6.85 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.8 (q), 20.7 (q), 22.0 (q), 25.5 (q), 27.3 (d), 42.3 (t), 48.4 (s), 55.6 (q), 113.1 (d), 119.2 (d), 119.8 (s), 120.6 (d), 129.8 (s), 136.7 (d), 138.0 (s), 141.8 (s), 154.9 (s), 170.0 (s), 207.3 (s); exact mass m/z calcd for $C_{19}H_{22}O_2$ 282.16199, found 282.16147.

(3a*R*,4*R*,5*S*)-4,5-Dihydroxy-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one (75). OsO_4 (50 mg, 0.2 mmol) and NMO (0.83 g, 6.9 mmol) were added to a stirred solution of olefin **74** (0.65 g, 2.3 mmol) in a mixture of CCl_4 (20 mL), water (5 mL), *t*-BuOH (20 mL), and acetone (30 mL), and stirring was continued for 12 h. Water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 25 cm), using 1:4 *t*-BuOMe−CH_2Cl_2, gave diol **75** [0.45 g, 81% corrected for recovered **74** (0.15 g, 23%)] as a colorless oil: FTIR ($CHCl_3$, cast) 3525, 2961, 1691, 1608 cm^{-1}; $[\alpha]_D$ = −245.4° (*c* 0.324, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 3 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.37 (d, J = 7.1 Hz, 3 H), 2.40 (s, 3 H), 2.47 (AB q, J = 18.1 Hz, $\Delta\nu_{AB}$ = 321.9 Hz, 2 H), 3.05 (s, 1 H), 3.16 (septet, J = 7.0 Hz, 1 H), 3.93 (s, 3 H), 4.04 (d, J = 4.4 Hz, 1 H), 4.36 (s, 1 H), 5.03 (d, J = 4.4 Hz, 1 H), 6.79 (s, 1 H), 6.94 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.0 (q), 20.5 (q), 21.9 (q), 22.1 (q), 26.1 (d), 46.1 (t), 46.4 (s), 55.6 (q), 66.5 (d), 73.1 (d), 112.7 (d), 121.4 (d), 121.6 (s), 131.5 (s), 138.8 (s), 144.6 (s), 158.6 (s), 163.9 (s), 208.1 (s); exact mass m/z calcd for $C_{19}H_{24}O_4$ 316.16745, found 316.16696.

(3a*R*,4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one (76). 2,6-Lutidine (1.0 mL, 8.50 mmol), followed by *t*-$BuMe_2SiOSO_2CF_3$ (1.3 mL, 5.55 mmol), was added by rapid injection to a stirred and cooled (0 °C) solution of diol **75** (0.43 g, 1.36 mmol) in CH_2Cl_2 (40 mL). The ice bath was removed, and stirring was continued for 4.5 h. Saturated aqueous NH_4Cl (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue

over silica gel (1.5 × 20 cm), using 1:19 EtOAc−hexane, gave ketone **76** (0.54 g, 73%) as a colorless oil: FTIR ($CHCl_3$, cast) 2956, 1698, 1631, 1608 cm^{-1}; $[\alpha]_D = -169.7°$ (*c* 0.254, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ −0.48 (s, 3 H), −0.03 (s, 6 H), 0.10 (s, 3 H), 0.70 (s, 9 H), 0.92 (s, 9 H), 1.08 (s, 3 H), 1.12 (d, $J = 7.0$ Hz, 3 H), 1.28 (d, $J = 7.1$ Hz, 3 H), 2.40 (s, 3 H), 2.61 (AB q, $J = 16.8$ Hz, $\Delta\nu_{AB} = 392.6$ Hz, 2 H), 2.84 (septet, $J = 7.0$ Hz, 1 H), 3.43 (d, $J = 2.7$ Hz, 1 H), 3.82 (s, 3 H), 5.12 (d, $J = 2.6$ Hz, 1 H), 6.68 (s, 1 H), 6.75 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.7 (q), −5.0 (q), −4.9 (q), −3.9 (q), 17.9 (s), 18.1 (s), 19.5 (q), 21.4 (q), 21.9 (q), 24.8 (q), 25.81 (q), 25.83 (q), 31.8 (d), 44.2 (t), 50.1 (s), 55.3 (q), 67.0 (d), 76.9 (d), 111.7 (d), 120.0 (d), 124.2 (s), 133.7 (s), 139.1 (s), 140.1 (s), 155.5 (s), 171.1 (s), 209.2 (s); exact mass *m*/*z* calcd for $C_{31}H_{52}O_4Si_2$ 544.34039, found 544.34002.

(3a*R*,4*R*,5*S*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-4,5-dihydro-3a*H*-cyclopenta[*a*]naphthalene (78) via Alcohol (77). DIBAL-H (1 M in cyclohexane, 2.0 mL, 2.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ketone **76** (0.47 g, 0.87 mmol) in CH_2Cl_2 (15 mL). After the addition, the ice bath was removed, and stirring was continued for 10 h. The mixture was recooled to 0 °C, $Na_2SO_4 \cdot 10H_2O$ (0.5 g) was added, and stirring was continued for 30 min. The resulting mixture was filtered through a Celite pad (1 × 2.5 cm), using CH_2Cl_2 as a rinse. The solvent was evaporated, and the residue (crude **77**) was dissolved in $ClCH_2CH_2Cl$ (40 mL).

Et_3N (0.8 mL, 5.74 mmol), followed by MsCl (0.2 mL, 2.57 mmol), was added to the stirred solution. Stirring was continued for 30 min, and the mixture was then refluxed for 4 h and cooled to room temperature. Saturated aqueous NH_4Cl (30 mL) was added, and the mixture was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using hexane, gave diene **78** (0.39 g, 84%) as a colorless oil: FTIR ($CHCl_3$, cast) 2958, 1607 cm^{-1}; $[\alpha]_D = +2.76°$ (*c* 0.290, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ −0.53 (s, 3 H), −0.02 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.66 (s, 9 H), 0.95 (s, 9 H), 0.98 (d, $J = 6.8$ Hz, 3 H), 1.06 (s, 3 H), 1.16 (d, $J = 7.0$ Hz, 3 H), 2.38 (s, 3 H), 2.84 (septet, $J = 6.8$ Hz, 1 H), 3.65 (d, $J = 2.9$ Hz, 1 H), 3.80 (s, 3 H), 5.02 (d, $J = 3.0$ Hz, 1 H), 6.22 (d, $J = 5.4$ Hz, 1 H), 6.53 (d, $J = 5.3$ Hz, 1 H), 6.51 (s, 1 H), 6.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.6 (q), −4.9 (q), −4.6 (q), −3.7 (q), 18.1 (s), 18.3 (s), 21.0 (q), 21.9 (q), 24.3 (q), 25.8 (q), 25.9 (q), 26.1 (q), 28.8 (d), 55.1 (q), 57.0 (s), 67.0 (d), 77.8 (d), 109.2 (d), 119.4 (d), 125.2 (s), 126.8 (d), 136.1 (s), 138.4 (s), 143.3 (s), 144.1 (d), 145.4 (s), 155.8 (s); exact mass *m*/*z* calcd for $C_{31}H_{52}O_3Si_2$ 528.34552, found 528.34448.

(1*R*,3a*R*,4*R*,5*S*,9b*R*)-4,5-Bis(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene (79). Pd−C (10%, 20 mg) was added to a solution of diene **78** (300 mg, 0.57 mmol) in MeOH−hexane (1:1, 20 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (39 psi) for 40 h. The mixture was then filtered through a Celite pad (1 × 2.5 cm), using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 × 20 cm), using hexane, gave compound **79** [217 mg, 78%, corrected for recovered **78** (24 mg, 8%] as a colorless oil: FTIR (CH_2Cl_2, cast) 2952, 1612 cm^{-1}; $[\alpha]_D = +37.7°$ (*c* 0.170, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ −0.14 (s, 3 H), 0.00 (s, 3 H), 0.09 (s, 3 H), 0.21 (s, 3 H), 0.46 (d, $J = 6.5$ Hz, 3 H), 0.83 (s, 9 H), 0.94 (s, 9 H), 1.02 (d, $J = 6.4$ Hz, 3 H), 1.14 (s, 3 H), 1.23−1.31 (m, 1 H), 1.36−1.42 (m, 1 H), 1.58−1.76 (m, 2 H), 1.88−1.97 (m, 1 H), 2.30 (s, 3 H), 2.75 (dd, $J = 7.3$, 12.7 Hz, 1 H), 2.94 (d, $J = 8.0$ Hz, 1 H), 3.35 (d, $J = 3.2$ Hz, 1 H), 3.77 (s, 3 H), 4.98 (d, $J = 3.1$ Hz, 1 H), 6.48 (s, 1 H), 6.62 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.2 (q), −4.9 (q), −4.8 (q), −3.0 (q), 18.5 (s), 18.7 (s), 20.4 (q), 21.8 (q), 24.4 (q), 26.1 (q), 26.26 (q), 26.31 (q), 27.9 (t), 33.0 (d), 34.1 (t), 44.0 (s), 52.9 (d), 54.4 (d), 54.8 (q), 66.7 (d), 77.5 (d), 107.9 (d), 123.2 (d), 125.0 (s), 137.3 (s), 139.0 (s), 156.5 (s); exact mass *m*/*z* calcd for $C_{27}H_{47}O_3Si_2$ $[M - C_4H_9]^+$ 475.30637, found 475.30630.

(1*R*,3a*R*,4*R*,5*S*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-diol (80). Bu_4NF (1.0 M, 3.0 mL, 3.0 mmol) was added to a stirred solution of compound **79** (0.20 g, 0.37 mmol) in THF (20 mL). The mixture was refluxed for 19 h, and then cooled to room temperature. Saturated aqueous NH_4Cl (15 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:3 EtOAc−hexane, gave diol **80** (98 mg, 85%) as white crystals: mp 145−147 °C; FTIR (CH_2Cl_2, cast) 3446, 2952, 1610 cm^{-1}; $[\alpha]_D = +82.0°$ (*c* 0.161, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.67 (d, $J = 6.6$ Hz, 3 H), 1.07 (d, $J = 6.3$ Hz, 3 H), 1.04−1.11 (m, 1 H), 1.16−1.24 (m, 1 H), 1.26 (s, 3 H), 1.48−1.56 (m, 2 H), 1.60−1.66 (m, 1 H), 1.85−1.93 (m, 1 H), 2.30 (s, 3 H), 2.36−2.42 (m, 1 H), 2.55 (s, 1 H), 2.97 (d, $J = 7.0$ Hz, 1 H), 3.49 (d, $J = 4.4$ Hz, 1 H), 3.83 (s, 3 H), 5.00 (d, $J = 4.5$ Hz, 1 H), 6.52 (s, 1 H), 6.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 21.5 (q), 21.9 (q), 24.0 (q), 26.5 (q), 28.0 (t), 31.1 (d), 32.8 (t), 44.2 (s), 52.6 (d), 53.6 (d), 55.4 (q), 65.6 (d), 74.7 (d), 108.3 (d), 122.9 (d), 123.2 (s), 137.7 (s), 137.9 (s), 157.9 (s); exact mass *m*/*z* calcd for $C_{19}H_{28}O_3$ 304.20386, found 304.20321.

(1*R*,3a*R*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[a]naphthalene-4,5-dione (81). DMSO (0.15 mL, 2.11 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise over ca. 5 min to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.15 mL, 1.68 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 30 min, and diol **80** (81 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 5 min. Stirring at −78 °C was continued for 1 h, and Et_3N (0.7 mL, 5.00 mmol) was added dropwise over ca. 2 min. Stirring was continued for 1 h, the dry ice bath was removed, and stirring was continued for 4 h. Saturated aqueous NH_4Cl (15 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc−hexane, gave diketone **81** (75 mg, 94%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2958, 1721, 1678, 1605 cm^{-1}; $[\alpha]_D = -187.1°$ (*c* 0.124, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.42 (d, $J = 6.4$ Hz, 3 H), 0.55 (d, $J = 6.6$ Hz, 3 H), 1.14−1.20 (m, 1 H), 1.25 (s, 3 H), 1.47−1.58 (m, 2 H), 1.73−1.81 (m, 1 H), 2.18−2.25 (m, 1 H), 2.38 (s, 3 H), 2.45−2.50 (m, 1 H), 3.32 (d, $J = 9.5$ Hz, 1 H), 3.90 (s, 3 H), 6.68 (s, 1 H), 6.75 (d, $J = 0.6$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.3 (q), 22.4 (q), 23.1 (q), 24.2 (q), 28.0 (t), 28.5 (d), 35.4 (t), 51.9 (d), 55.1 (s), 55.97 (q), 56.04 (d), 110.9 (d), 120.6 (s), 124.3 (d), 145.9 (s), 147.1 (s), 161.4 (s), 180.8 (s), 201.7 (s); exact mass *m*/*z* calcd for $C_{19}H_{24}O_3$ 300.17255, found 300.17218.

(1*R*,3a*R*,9b*R*)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-2,3,-3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione (82). LiCl (dried under oilpump vacuum at 100 °C, 29 mg, 0.68 mmol) was added to a stirred solution of diketone **81** (45 mg, 0.15 mmol) in DMF (10 mL). The mixture was then refluxed for 20 h, cooled, diluted with water (15 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:9 EtOAc−hexane containing 1%v/v MeOH, gave phenol **82** (37 mg, 87%) as yellow crystals: mp 108−109 °C; FTIR (CH_2Cl_2, cast) 2958, 1725, 1633, 1566 cm^{-1}; $[\alpha]_D = -203.1°$ (*c* 0.128, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.41 (d, $J = 6.5$ Hz, 3 H), 0.53 (d, $J = 6.6$ Hz, 3 H), 1.14−1.22 (m, 1 H), 1.28 (s, 3 H), 1.48−1.56 (m, 1 H), 1.62−1.71 (m, 1 H), 1.74−1.83 (m, 1 H), 2.22−2.30 (m, 1 H), 2.36 (s, 3 H), 2.61 (ddd, $J = 5.5$, 7.7, 13.1 Hz, 1 H), 3.38 (d, $J = 9.1$ Hz, 1 H), 6.67 (t, $J = 0.7$ Hz, 1 H), 6.73 (s, 1 H), 11.9 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8 (q), 22.5 (q), 23.1 (q), 24.4 (q), 26.9 (t), 28.1 (d), 33.8 (t), 51.4 (d), 56.5 (q), 56.8 (s), 116.2 (d), 116.7

(s), 123.3 (d), 144.1 (s), 150.7 (s), 164.6 (s), 184.3 (s), 200.0 (s); exact mass *m*/*z* calcd for $C_{18}H_{22}O_3$ 286.15689, found 286.15670.

(1*R*,3a*R*,9b*R*)-7-Bromo-6-hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(−)-Hamigeran B] (1). A solution of NBS (2.5 mg, 0.015 mmol) in CH_2Cl_2 (1 mL) was added dropwise over ca. 10 min to a stirred and cooled (0 °C) solution of phenol **82** (4 mg, 0.014 mmol) and dry *i*-Pr_2NH (ca 0.01 mL, 0.07 mmol) in CH_2Cl_2 (2 mL). The cold bath was removed after the addition, and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm), using 1:19 *t*-BuOMe-hexane, containing 1%v/v MeOH, gave hamigeran B (**1**) (4.5 mg, 88%) as a yellow solid: 165−167 °C; FTIR (CH_2Cl_2, cast) 2956, 1724, 1633, 1609 cm^{-1}; $[\alpha]_D = -176.4°$ (*c* 0.142, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.44 (d, J = 6.5 Hz, 3 H), 0.53 (d, J = 6.6 Hz, 3 H), 1.15−1.23 (m, 1 H), 1.28 (s, 3 H), 1.49−1.59 (m, 1 H), 1.63−1.72 (m, 1 H), 1.75−1.85 (m, 1 H), 2.25−2.33 (m, 1 H), 2.50 (s, 3 H), 2.62 (ddd, J = 5.5, 7.7, 13.1 Hz, 1 H), 3.38 (d, J = 9.2 Hz, 1 H), 6.82 (s, 1 H), 12.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.7 (q), 23.3 (q), 24.3 (q), 24.4 (q), 26.7 (t), 28.1 (d), 33.8 (t), 51.3 (d), 56.2 (q), 56.9 (s), 111.5 (s), 117.2 (s), 124.2 (d), 142.7 (s), 150.2 (s), 160.8 (s), 184.4 (s), 199.0 (s); exact mass *m*/*z* calcd for $C_{18}H_{21}{}^{79}BrO_3$ 364.06741, found 364.06791.

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Supporting Information Available: NMR spectra of all new compounds except intermediates **22**, **23**, **40**, **54**, **77**; X-ray data for **25**, **43**, **57**; and procedures for the synthesis of **13**−**15**, **30**, **32**−**38**, **45**−**52**, **54**−**59**, (±)-**1**, **61**, and **63**. This material is available free of charge via the Internet at http://pubs.acs.org.

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