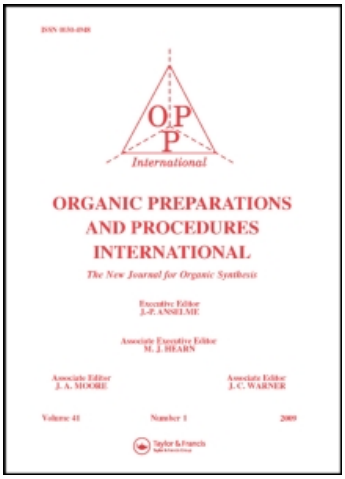

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF THE HAMIGERANS. A REVIEW

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To cite this Article Clive, Derrick L. J. and Wang, Jian(2005) 'SYNTHESIS OF THE HAMIGERANS. A REVIEW', Organic Preparations and Procedures International, 37: 1, 1 — 35
To link to this Article: DOI: 10.1080/00304940509355400
URL: http://dx.doi.org/10.1080/00304940509355400

ORGANIC PREPARATIONS AND PROCEDURES INT., 37 (1), 1-35 (2005)

SYNTHESIS OF THE HAMIGERANS. A REVIEW

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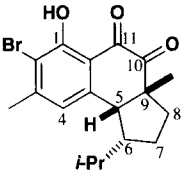
INTRODUCTION

Isolation and Structure Determination

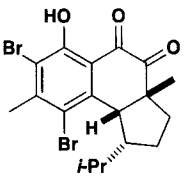
In a long series of publications, Cambie and his colleagues have described numerous natural products isolated from marine sponges. Part 19 of the series[1] is especially noteworthy since it reports the structures of a group of compounds that includes a substance — hamigeran B (**1**) — which shows very impressive activity against polio and herpes viruses. The compounds were isolated from a marine sponge collected in shallow water off the north east coast of New Zealand. A total of eight compounds were obtained from the sponge; they have the structures **1-8** shown in *Scheme 1*.

The compounds are obviously related, and establishment of their biogenesis would be expected to reveal an interwoven pattern; nothing, however, has yet been published on this subject. The sponge, *Hamigera tarangaensis* Bergquist and Fromont (family Anchinoidae, syn. Phorbasidae) comes from a family that has been very little investigated for secondary metabolites. However, the Anchinoidae are clearly a promising source of biologically active compounds and represent worthwhile subjects for study, since other members of the family are the sources of the cytostatic macrolides called phorbazoles,[2,3] and of the dimeric peptide alkaloids anchinopeptolides,[4] which inhibit receptors for somatostatin, human B2 bradykinin, and neuropetide Y.

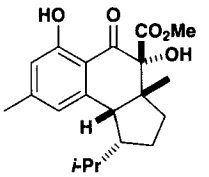
Compounds **1-8** were obtained from a methanol extract of the freeze-dried sponge, and in each case the isolated substance represented less than 1% of the dried sponge weight. The structures were established mainly by spectroscopic methods and, in the case of hamigeran A (**4**) by X-ray analysis,[5] which also gave the absolute configuration. The evident family relationship was used to assign the absolute configuration to hamigeran B (**1**) — an assignment now confirmed by synthesis — and to compounds **2**, **3**, **5**, **7** and **8**. The structure of **6** was established by X-ray analysis[5] of a decomposition product (**9**), and the absolute stereochemistry was assigned on the assumption that no stereochemical inversion occurred during formation of **9**.



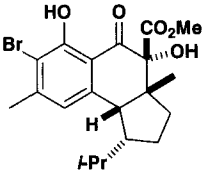
1 hamigeran B



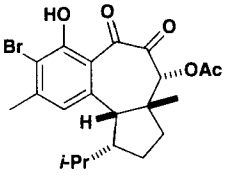
2 4-bromohamigeran B



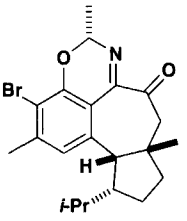
3 debromohamigeran A



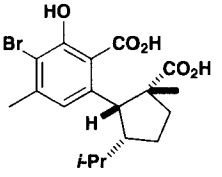
4 hamigeran A



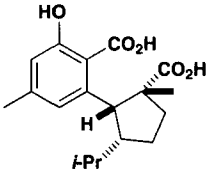
5 hamigeran C



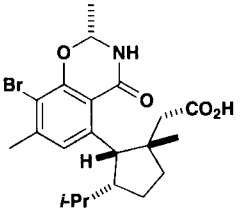
6 hamigeran D



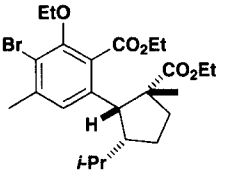
7 hamigeran E



8 debromohamigeran E



9 decomposition product from hamigeran D



10 derivative of hamigeran E

Scheme 1

Compounds **1-6**, acid **9** (the decomposition product of **6**), and the *bis*-ester **10** (derived from hamigeran E) were subjected to a number of biological screens. Hamigeran D (**6**) had the strongest *in vitro* antitumor activity against P-388, with an IC_{50} of 8 μM. Hamigeran B (**1**), 4-bromohamigeran B (**2**) and hamigeran C (**5**) had IC_{50} values of 13.5, 13.9 and 16.8 μM, respectively. Hamigeran A (**4**), and compounds **9** and **10** were only weakly cytotoxic. None of the compounds tested (*i. e.* presumably only **1-6**, **9** and **10**) were active against the Gram-negative bacterium *E. coli* or the yeast *Candida albicans*, and no antimicrobial activity was shown by **4** or **10**. Against the Gram-positive bacterium *Bacillus subtilis*, compounds **5**, **6**, and **9** all showed a 3 mm inhibition zone outside the disk at assay loadings of 96, 150, and 156 μg, respectively. With **1** and **2** inhibition was slight, and completely absent with **4** and **10**. The three substances **1**, **5** and **6** showed slight activity against *Trichophyton mentagrophytes*.

The most conspicuous biological activity was observed in antiviral assays. Hamigeran B (**1**) showed 100% virus inhibition against Herpes and Polio viruses at a concentration of 132 μg per disk. Little cytotoxic activity was evident, but none of the other compounds showed any antiviral activity.

The hamigerans have attracted much attention from synthetic chemists for a number of clearly identifiable reasons: the compounds represent a new structural type, one member of the

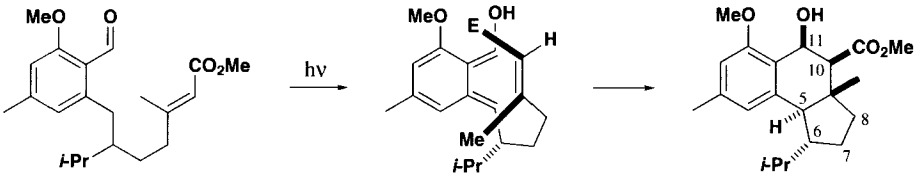
family has exceptional biological activity, and it was obvious that synthetic work in this area would have to solve a severe stereochemical problem associated with the orientation of the isopropyl group. This group extends towards the concave face of hamigeran A and B, and the X-ray analysis of **4** shows that the C(4) aromatic hydrogen is quite close to the methine hydrogen of the isopropyl substituent and to one of its methyl groups (2.28 Å and 2.24 Å, respectively).

I. SYNTHESIS OF HAMIGERANS by Nicolaou, Gray and Tae

The first syntheses of hamigerans were reported[6] by the Nicolaou group, who described routes to hamigeran A (**4**), debromohamigeran A (**3**), hamigeran B (**1**), 4-bromohamigeran B (**2**), and hamigeran E (**7**), as well as several unnatural analogs.

To a synthetic chemist, formation of bromohamigeran B by bromination of hamigeran B is an obvious approach, as is conversion of debromohamigeran A into hamigeran A. Further analysis of the synthetic problems would probably have revealed that hamigeran E (**7**) might be accessible by appropriate bond cleavage of hamigeran B (**1**), with or without protection of the phenolic hydroxyl. Finally, selection of debromohamigeran A (**3**) as the primary target would set the stage for a sequence whereby both bromohamigeran A and hamigeran B might be reached — the former, obviously, by direct bromination, and the latter by converting the α-hydroxy ester unit of **3** into a carbonyl group. In the event the route did indeed follow this sequence of inter-conversions.

The approach[6c] was based on a process of photoenolization and intramolecular Diels-Alder cycloaddition, along the lines summarized in *Scheme 2*.



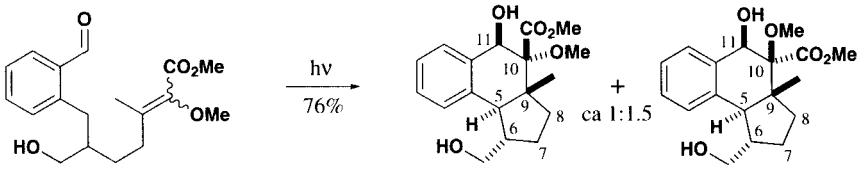
2.1 **2.2** E = CO_2Me **2.3**

Scheme 2

The advantage of this approach is that a tricyclic skeleton (*cf.* **2.3**) is easily constructed from a starting material (see **2.1**) that itself should be readily accessible; a disadvantage, however, is that the stereochemical outcome of the Diels-Alder reaction (**2.2** → **2.3**) led to *trans* ring fusion, so that stereochemical adjustment was required. This posed additional problems, although all were solved, and the photoenolization-intramolecular Diels-Alder path was shown to be a very useful general reaction.

Initial studies[6c] on the photochemical Diels-Alder route to hamigerans included the preparation of **3.1** (*Scheme 3*) as a 1:1.5 mixture of *Z* and *E* isomers. On photolysis, **3.2** and **3.3** (1:1.5) were obtained in a combined yield of 76%. The *trans* ring fusion was expected on the basis of many model studies on this type of Diels-Alder reaction, but the incorrect relative stereo-

chemistry at C(10) — *irrespective of the isomer ratio in the starting material* — was an unwelcome surprise. It was not possible to establish if the initial olefin underwent *E/Z* isomerization

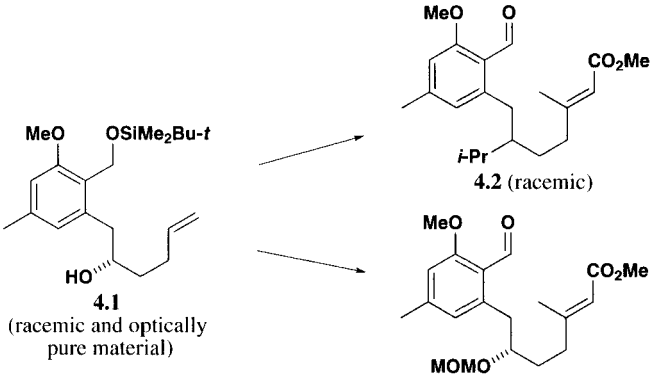


3.1 Z:E ca 1:1.5 **3.2** **3.3**

Scheme 3

during the reaction, since the *E/Z* isomers of the starting material were not separable and, moreover, an additional pathway for scrambling the C(10) stereochemistry was later discovered (see *Scheme 8*).

The two other cyclization precursors (±)-**4.2** and (–)-**4.3** were also considered[6c] in order to explore ways of solving the problem of setting up the correct relative stereochemistry at C(5), C(6), C(9) and C(10). The first of these [(±)-**4.2**] would be used in studies aimed at controlling relative stereochemistry, while the optically pure intermediate [(–)-**4.3**] was destined to be used to make a single hamigeran enantiomer by a route that would allow stereochemical control at C(5), such control being mediated by the adjacent oxygen function (in the form of a ketone). Both (±)-**4.2** and (–)-**4.3** would be made from the structurally common intermediate **4.1**, which was prepared in both its racemic and levorotatory form (shown).



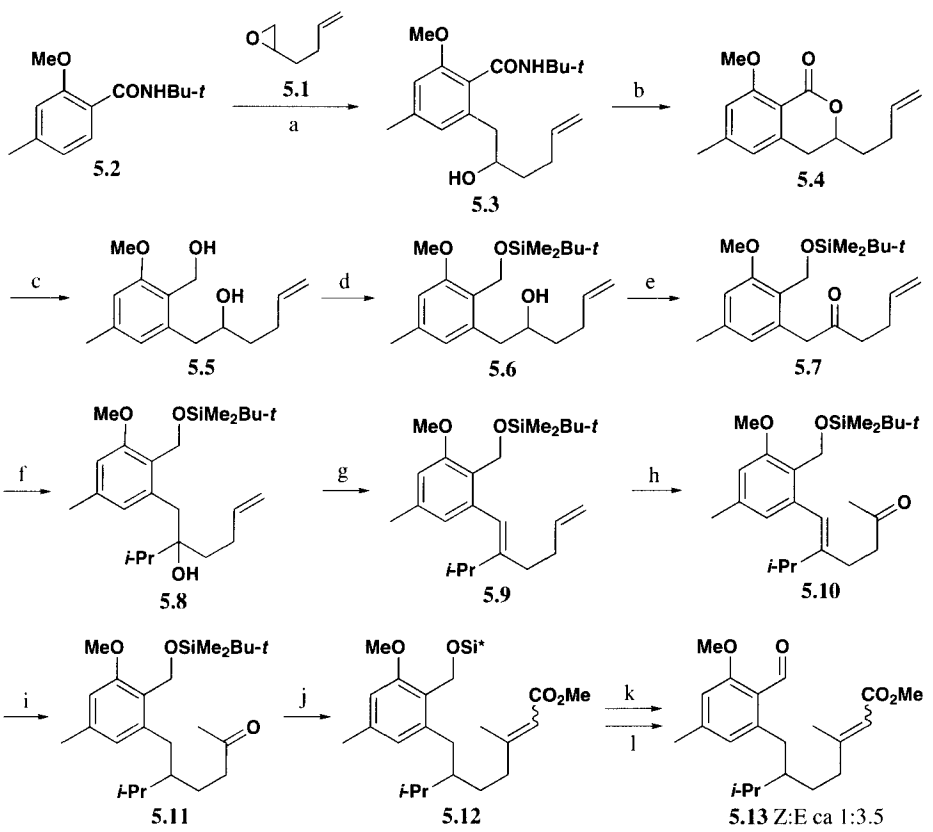
4.1
(racemic and optically pure material)

4.2 (racemic)

4.3 (optically pure)

Scheme 4

For the intended studies with (±)-**4.2**, the commercially available racemic epoxide **5.1** was used as the starting material.[6c] *ortho*-Lithiation of **5.2** and reaction with the epoxide gave the expected alcohol **5.3**, which was converted by acid-catalyzed cyclization into lactone **5.4**. Reduction ($LiAlH_4$) and selective silylation then produced the key intermediate **5.6**. Oxidation afforded the corresponding ketone **5.7**, which was ready for introduction of the isopropyl group. Not surprisingly, *i*-PrMgCl itself was unsuitable, but the corresponding less basic cerium species was very effective, and yielded tertiary alcohol **5.8** in high yield (94%). Low temperature (–50 to

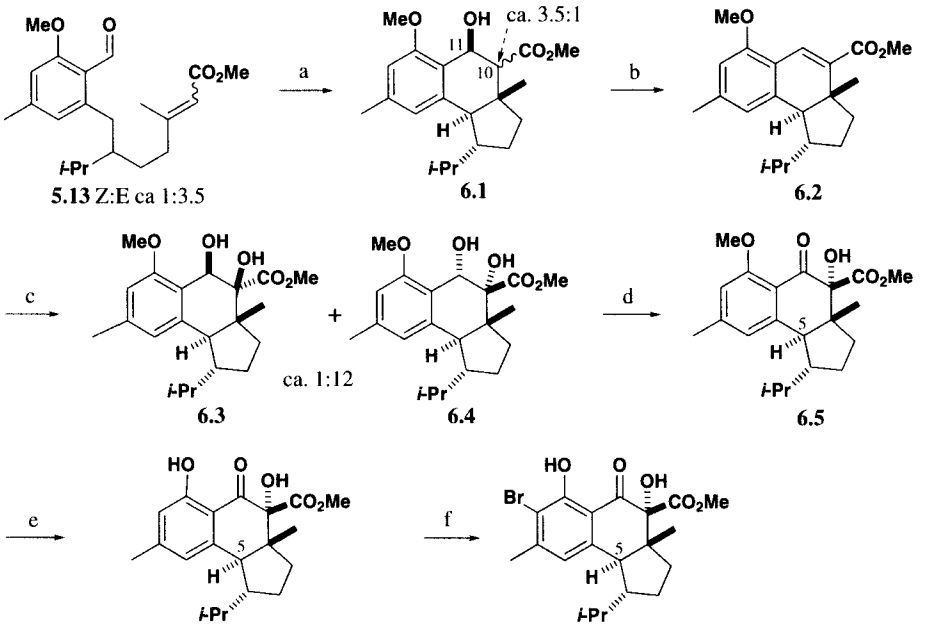


Reagents and conditions: a) *t*-BuLi, TMEDA-THF, **5.1**, 69%; b) TsOH, PhH, heat, 91%; c) $LiAlH_4$, THF, 91%; d) *t*-$BuMe_2SiCl$, Et_3N, CH_2Cl_2, DMF, 89%; e) SO_3•pyr, DMSO, CH_2Cl_2, 94%; f) *i*-PrMgCl, $CeCl_3$, THF, 94%; g) $SOCl_2$, pyr, CH_2Cl_2, –50°C to –20°C, 80%, h) $Pd(OAc)_2$, $Cu(OAc)_2$, O_2, DMA, water, 81%; i) Pd/C, $NaHCO_3$, EtOAc, H_2, 95%; j) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 94%, *Z*/*E* ca. 1:3.5; k) HF•py, THF, 91%; l) SO_3•pyr, DMSO, Et_3N, 88%

Scheme 5

–20°C) dehydration with $SOCl_2$-pyridine gave the aryl-conjugated olefin **5.9** which was largely (>10:1) a single geometrical isomer. The geometry was not established, and an arbitrary assignment is shown in **5.9**. Wacker oxidation served to convert the terminal double bond into a methyl ketone (**5.9** → **5.10**), and hydrogenation in the presence of solid sodium bicarbonate then gave the saturated ketone **5.11**. This was homologated by the Horner-Emmons-Wadsworth method to **5.12**, which was obtained as a 3.5:1 mixture of geometrical isomers. Desilylation under rather specifically defined conditions (HF•pyridine, THF, 25°C, 40 min, 91%) released the parent alcohols, and oxidation (SO_3•pyridine, Et_3N, DMSO) gave aldehydes **5.13** as an ca 1:3.5 mixture of *Z* and *E* isomers.

When the aldehydes were photolyzed in deoxygenated benzene, using a high pressure mercury lamp and a Pyrex filter, the tricycles **6.1** were obtained as a 3.5:1 mixture of C(10) epimers.[6c] This result was expected, because of the presence of double bond isomers in **5.13**.



5.13 Z:E ca 1:3.5

6.1

6.2

6.3

6.4

6.5

6.6 (±)-5-epi-debromohamigeran A

6.7 (±)-5-epi-hamigeran A

Reagents and conditions: a) hv, 91%; b) HCl, MeOH, 90%; c) OsO_4, NMO, 91% of **6.4**; d) SO_3•pyr, DMSO, Et_3N, CH_2Cl_2, 88%; e) BBr_3, THF, –78°C, 96%; f) NBS, *i*-Pr_2NH, 90%

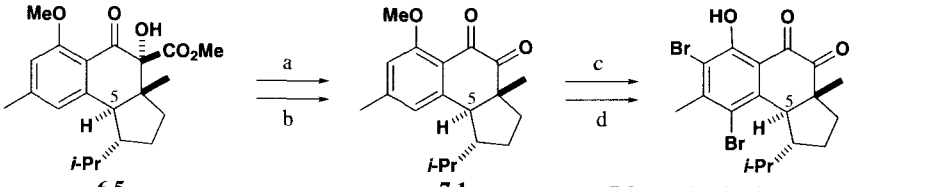
Scheme 6

Both tricyclic isomers are equally useful, as C(10) and C(11) are next converted to sp^2 hybridization by exposure of the mixture to the action of methanolic HCl (**6.1** → **6.2**).

At this point a number of functional group manipulations were carried out. Dihydroxylation with OsO_4-NMO gave diols **6.4** and **6.3** (ca 12:1) in a combined yield of 92%. The benzylic hydroxyl of the major isomer was oxidized, again using the SO_3•pyridine-DMSO reagent (**6.4** → **6.5**), and demethylation with BBr_3 afforded 5-*epi*-debromohamigeran A (**6.6**). A number of (non-specified) attempts to epimerize **6.6** at C(5) were unsuccessful, as were related experiments with several of its precursors.

Although this initial route did not give a natural hamigeran, it did provide an opportunity to prepare analogs for biological testing. Accordingly, **6.6** was subjected to regioselective bromination (**6.6** → **6.7**), using the NBS-*i*-Pr_2NH combination, which was known[7] to react at the *ortho* position of phenols. In the present case it was shown that bromination is not regioselective in the absence of *i*-Pr_2NH (5-10 mole%).

Several other 5-*epi*-analogs were also prepared.[6c] Ester hydrolysis of **6.5** (KOH, MeOH) and periodate cleavage of the resulting α-hydroxy acid gave diketone **7.1** (65% overall). Demethylation (BBr_3, –78°C) and *bis*-bromination (NBS, DMF) yielded **7.2** (94% overall).



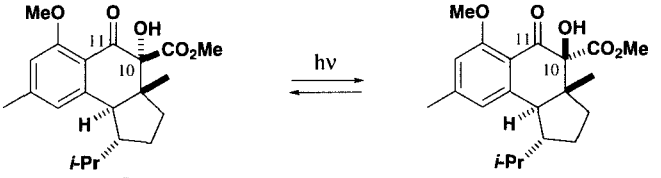
6.5 **7.1** **7.2** (±)-5-epi-4-bromohamigeran B

Reagents and conditions: a) KOH, MeOH; b) Bu_4NIO_4, 65% overall; c) BBr_3; d) NBS, DMF, 94% overall

Scheme 7

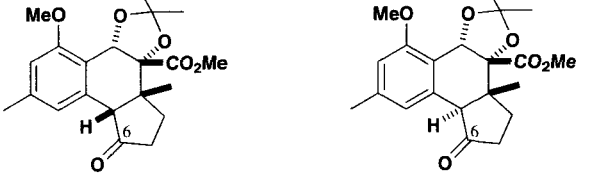
a) The C(5) Stereochemistry Problem

One of the experiments tried in order to invert the C(5) stereochemistry involved UV irradiation of **6.5** in benzene.[6c] This process resulted in a 1:3 mixture of the starting material and its C(10) epimer (**8.1**). Presumably, Norrish Type I homolysis of the C(10)-C(11) bond and reclosure of the resulting diradical is involved. The same experiment with **6.6**, the phenol derived from **6.5**, did not produce any epimerization at C(10).



6.5 **Scheme 8** **8.1**

Attempts to effect epimerization at C(5) were eventually abandoned, in part, because at this point molecular modeling indicated that the desired C(5) epimer of **6.5** is less stable than **6.5** itself.[6c] Computational studies also revealed a marked difference in the relative strain energies of **9.1** (19.65 kcal/mol) and **9.2** (24.72 kcal/mol), two compounds in which the C(6) sp^3 center of

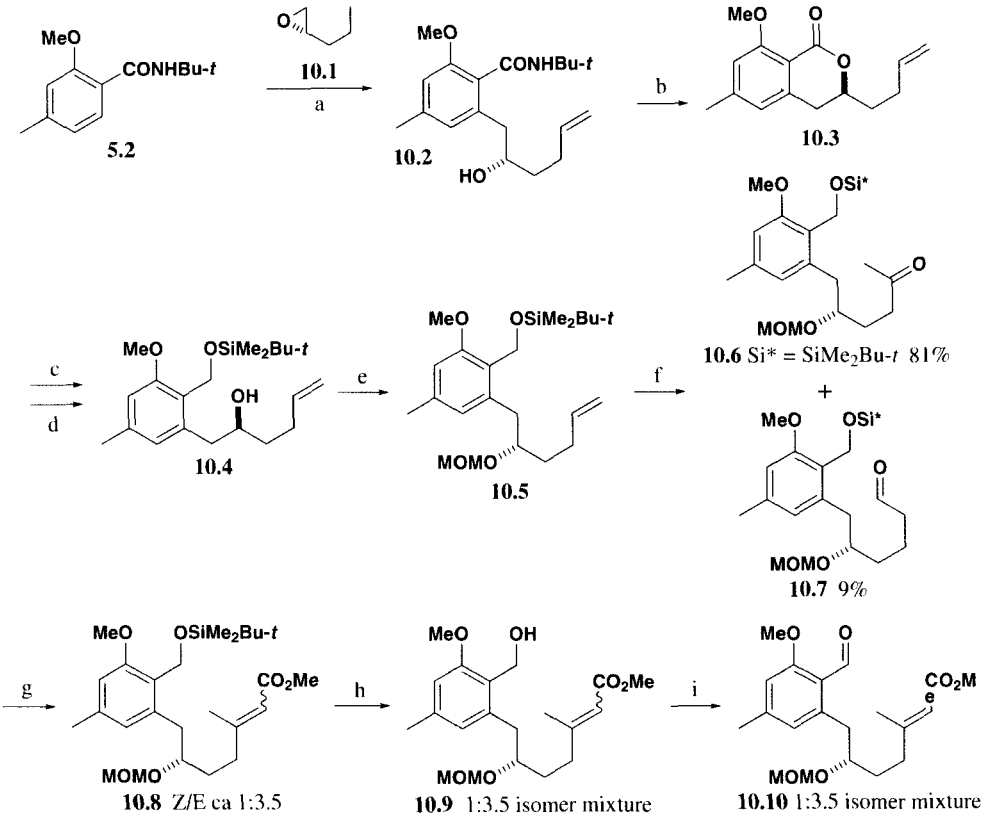


9.1 **Scheme 9** **9.2**

the hamigerans has been replaced by an sp^2 carbon and, of course, a bulky isopropyl group has been replaced by a carbonyl oxygen, so that a number of steric interactions in the natural compounds are now absent. The calculations show that the desired *cis* ring fusion should be significantly more stable.[6c]

As indicated earlier, the other starting material considered for the photocyclization was (–)-**4.3**. Its synthesis began with **5.2**, and the first few steps followed the earlier work (see

Scheme 5) that had been done with racemic compounds. *ortho*-Metallation of **5.2** (*Scheme 10*)[6c] and condensation with optically active (99% ee) epoxide **10.1** gave the lactone, after acid-catalyzed cyclization of the initial adduct (**5.2** → **10.2** → **10.3**). Reduction ($LiAlH_4$) and selective protection (*t*-$BuMe_2SiCl$) then gave alcohol **10.4**. Protection of the free hydroxyl as its

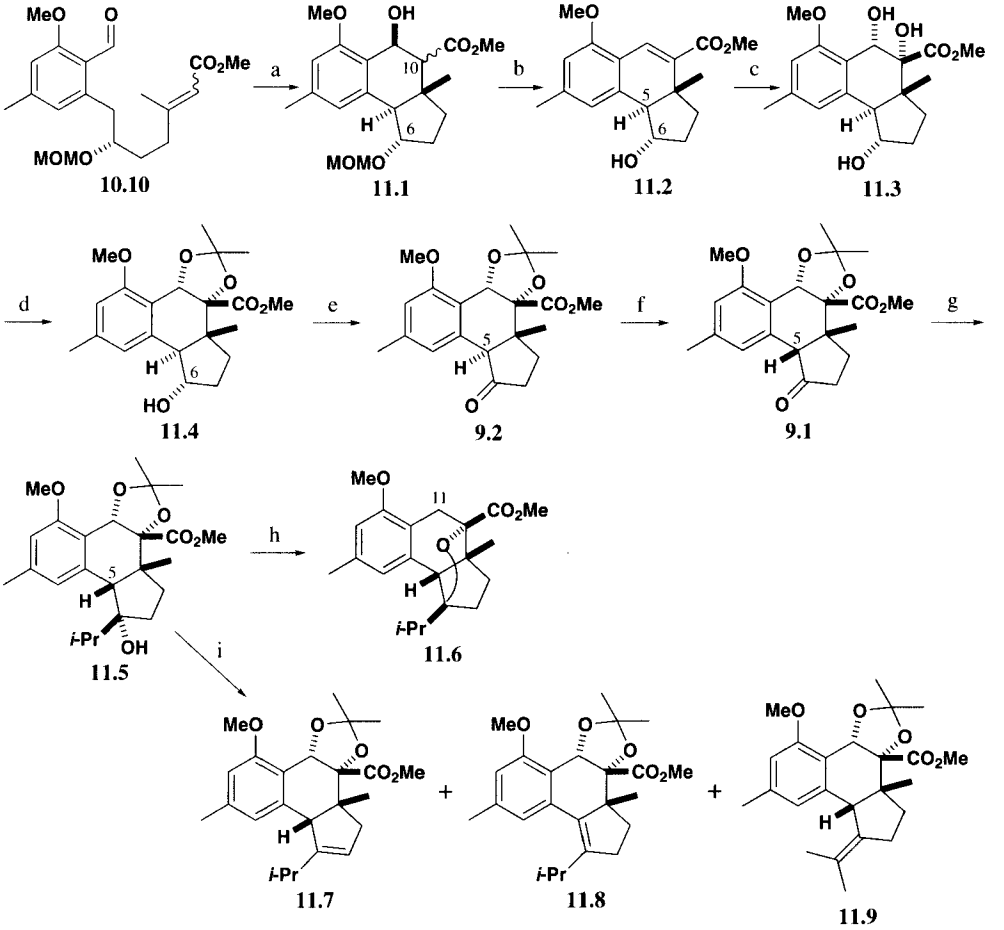


Reagents and conditions: a) *t*-BuLi, TMEDA-THF, **10.1**, 69%; b) TsOH, PhH, heat, 91%; c) $LiAlH_4$, THF, 91%; d) *t*-$BuMe_2SiCl$, Et_3N, CH_2Cl_2, DMF, 89%; e) MOMCl, *i*-Pr_2NEt, 83%; f) $Pd(OAc)_2$, $Cu(OAc)_2$, O_2, DMA, water, 81%; g) $(MeO)_2P(O)CH_2CO_2Me$, NaH, 94%; h) HF•pyr, THF, 20 min, 91%; i) SO_3•pyr, DMSO, Et_3N, 92%

Scheme 10

MOM ether, and Wacker oxidation took the route as far as ketone **10.6**. In the oxidation step (81%) a small amount (9% yield) of aldehyde **10.7** was also formed. The intermediate olefin **10.5** had an ee of greater than 98.5%. Horner-Emmons-Wadsworth reaction now produced **10.8** as an ca 1:3.5 mixture of *Z* and *E* isomers in a combined yield of 94%. Desilylation (**10.8** → **10.9**) was achieved (91%) by treatment with HF•pyridine in THF under carefully controlled conditions. With long reaction times the double bond moved out of conjugation, and could not be moved back. The same deconjugation had been observed with **5.12**, but in that case the tendency was less pronounced. Oxidation of **10.9** with SO_3•pyridine-DMSO-Et_3N generated **10.10**, the substrate for the key photoenolization-intramolecular Diels-Alder reaction. When that experi-

ment was tried it gave in high yield the expected C(10) epimers **11.1**.[6c] Treatment with warm methanolic HCl caused dehydration and deprotection, and **11.2** was obtained in 85% overall yield from **10.10**. Compound **11.2** is the second key intermediate, the hope — ultimately realized — being that the C(6) oxygen function would provide opportunities for effecting epimerization at C(5). The route leading to **11.2** provides a method for making an advanced intermediate with an ee over 99% from a very simple starting material — the optically pure epoxide **10.1**.



Reagents and conditions: a) benzene, hv; b) 1% anhydrous HCl in MeOH, 60°C, 85% from **10.10**; c) OsO_4, NMO, THF-*t*-BuOH-H_2O-pyridine, 94% (ca 12:1 diastereoselectivity); d) (i) 2-methoxypropene, pyridinium *p*-toluenesulfonate, CH_2Cl_2, 0°C; (ii) TsOH, MeOH, 0°C, 93%; e) Dess-Martin periodinane, CH_2Cl_2, 0°C; f) DBU, CH_2Cl_2, 0°C, 93% for two steps; g) *i*-PrMgCl, $CeCl_3$, –78°C → 0°C, 95%; h) Et_3SiH, CF_3CO_2H, CH_2Cl_2, 25°C, 65%; i) $SOCl_2$, pyridine, 2,6-lutidine, CH_2Cl_2, –50°C → –20°C, 94% [**11.7** (77%), **11.8** (11%), **11.9** (6%)]

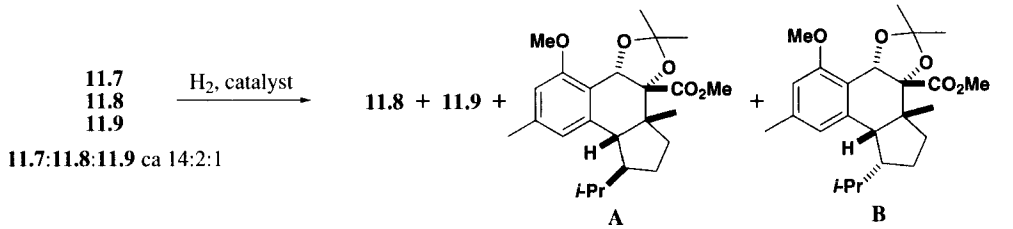
Scheme 11

As in the studies leading to 5-*epi*-hamigeran A (see *Scheme 6*), olefin **11.2** was dihydroxylated (**11.2** → **11.3**) with good facial selectivity (ca 12:1 in favor of **11.3**), and the desired isomer could be isolated in 86% yield. Protection of the vicinal hydroxyl groups as an acetonide

(**11.3** → **11.4**) was achieved under standard conditions, but additional treatment with $TsOH•H_2O$ in MeOH was required in order to hydrolyze a hemiketal formed by the C(6) hydroxyl. Oxidation of this hydroxyl with the Dess-Martin reagent (**11.4** → **9.2**) set the stage for epimerization at C(5) and, in the event, brief exposure to DBU at 0°C gave the desired *cis*-fused ketone **9.1** in 93% yield (from **11.4**). The facility of the epimerization is consistent with the large strain energy difference calculated for **9.1** and **9.2**. Treatment with the reagent generated from *i*-PrMgCl and $CeCl_3$ resulted in attack from the convex face and gave the tertiary alcohol **11.5**.

The next order of business was to remove the hydroxyl. Reductive elimination with Et_3SiH-CF_3CO_2H afforded the cyclic ether **11.6**, a transformation that hints at the lability of the C(11) oxygen function. However, reaction of alcohol **11.5** with $SOCl_2$-2,6-lutidine-pyridine at low temperature produced a mixture of the trisubstituted olefin **11.7** (77%) together with small amounts of the isomeric olefins **11.8** (11%) and **11.9** (6%).

Disappointingly, hydrogenation of the olefin mixture did not proceed as desired, even though considerable effort[6c] was devoted to this step, involving the use of a variety of catalysts and conditions [PtO_2 (EtOAc, 3 atm of H_2), $Pd(OH)_2$ (EtOH, 3 atm of H_2), 10% Pd-C EtOAc, 50 atm of H_2), $Rh\text{-}Al_2O_3$ (EtOH, 50 atm of H_2), rhodium black (EtOH, 20 atm of H_2), $IrPCy_3(COD)(pyr)PF_6$ (CH_2Cl_2, 10 atm of H_2)]. With the last two catalysts, hardly any reaction occurred, but with the others the desired *exo* hydrogenation product was never formed in satisfactory amount, the product distribution being as shown in *Table 1*. It is interesting to note that in



11.7:**11.8**:**11.9** ca 14:2:1

Table 1.

		11.8	**11.9**	**A**	**B**
i	PtO_2	6	3	71	20
ii	$Pd(OH)_2$	24	10	50	15
iii	10% Pd-C	40	7	33	19
iv	$Rh\text{-}Al_2O_3$	7	3	6	21

other work published by the Trost group (*see later*), a substance with a trisubstituted double bond, corresponding to the one in **11.7**, was cleanly hydrogenated in the desired stereochemical sense over Ir black. In some experiments (*Table 1*, entries ii and iii) the proportion of tetrasubstituted olefins was higher than in the starting material, suggesting that isomerization of the trisubstituted double bond into a tetrasubstituted position is a significant pathway. Extensive recovery of the tetrasubstituted olefins indicates the resistance of such species to hydrogenation. Examina-

tion of physical models and computational modeling of **11.7** suggest that one of the isopropyl methyl groups blocks access to the α-face of the molecule (see *Figure 1*).

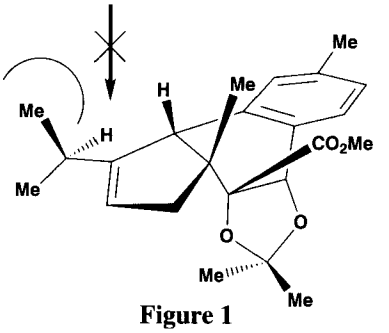
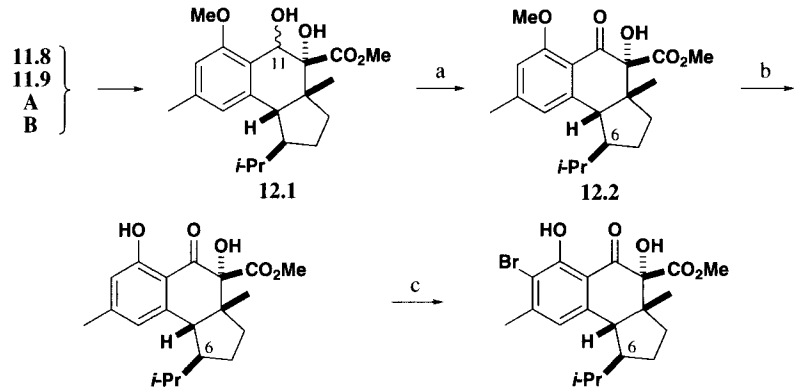


Figure 1

Once again, having reached an advanced intermediate belonging to an unnatural series, in this case the 6-*epi* isomers, the Nicolaou group decided to make several of the derived 6-*epi*-hamigerans; such compounds would be useful for biological testing and their preparation would provide experience that was likely to be of value in the synthesis of the natural compounds.

To this end, a mixture from one of the hydrogenation experiments (the experiment of *Table 1*, entry i) was heated with hydrochloric acid in THF.[6c] Both ketal hydrolysis and epimerization at C(11) occurred to afford **12.1** as the main product (*Scheme 12*). The crude mixture was



12.1

12.2

12.3 6-epi-debromohamigeran A

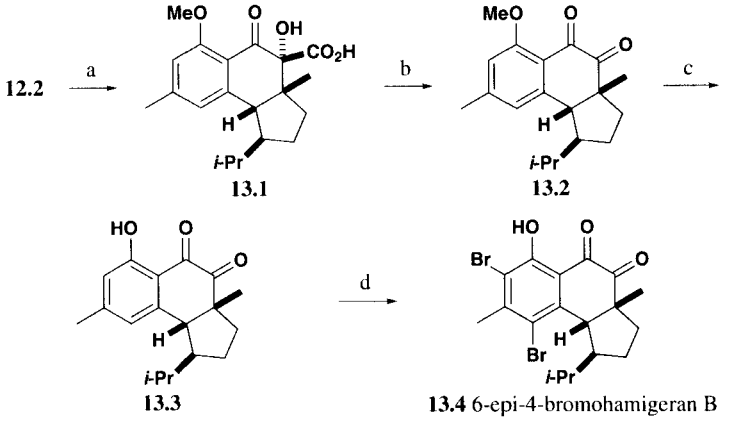
12.4 6-epi-hamigeran A

Reagents and conditions: a) SO_3•pyr, DMSO, CH_2Cl_2, Et_3N, 93%; b) BBr_3, CH_2Cl_2, –78°C, 93%; c) NBS, *i*-Pr_2NH, CH_2Cl_2, 0°C, 94%

Scheme 12

oxidized (SO_3•pyridine-DMSO) and careful chromatography then allowed isolation of ketone **12.2** in 45% overall yield from the hydrogenation substrate mixture. None of the corresponding ketone with the natural C(6) stereochemistry was isolated, even though the appropriate precursor was present in the hydrogenation mixture. Had such a ketone been isolable it would have immediately permitted some exploratory experiments aimed at the natural hamigerans. Later, a possible reason was discovered for the absence of material with the natural C(6) stereochemistry (see below, discussion of the reactions in *Scheme 14*).

Deprotection of the phenolic *O*-methyl ether with BBr_3 at –78°C gave 6-*epi*-debromohamigeran A (**12.3**), and 6-*epi*-hamigeran A (**12.4**) was then made by bromination *ortho* to the phenolic hydroxyl (NBS, *i*-Pr_2NH). Hydrolysis of the ester group (KOH) of **12.2** gave access to 6-*epi*-4-bromohamigeran B (**13.4**) by the sequence (**13.1** → **13.2** → **13.3** → **13.4**) summarized in *Scheme 13*.[6c]

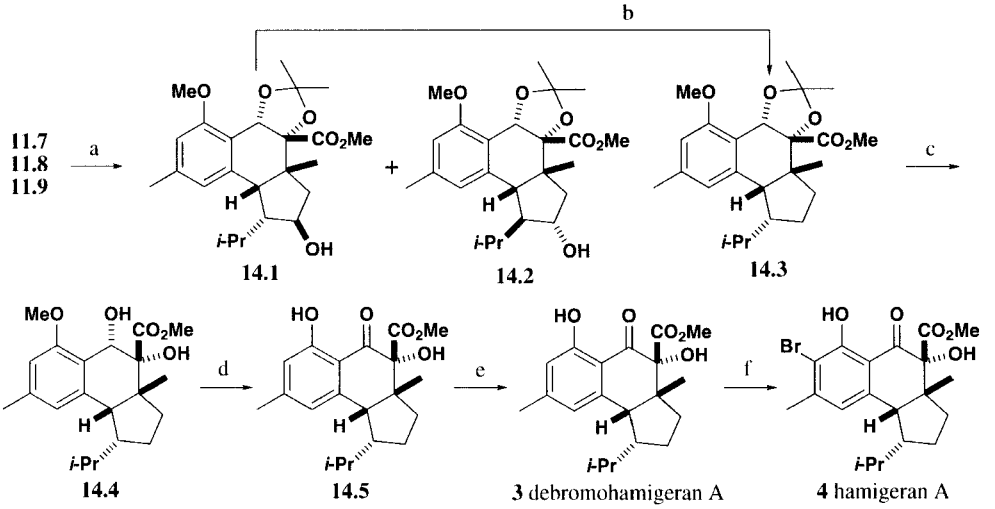


Reagents and conditions: a) aq. KOH, MeOH, 70°C; b) *n*-Bu_4NIO_4, dioxane, 100°C, 65% overall; c) BBr_3, CH_2Cl_2, 100%; d) NBS, DMF, 93%

Scheme 13

b) *The Final Successful Approach*

Olefin **11.7** (in admixture with **11.8** and **11.9**, 14:2:1) was subjected to hydroboration with BH_3•SMe_2 with sonication at 40°C.[6c] Oxidative workup gave **14.1** in 45% yield and **14.2** in



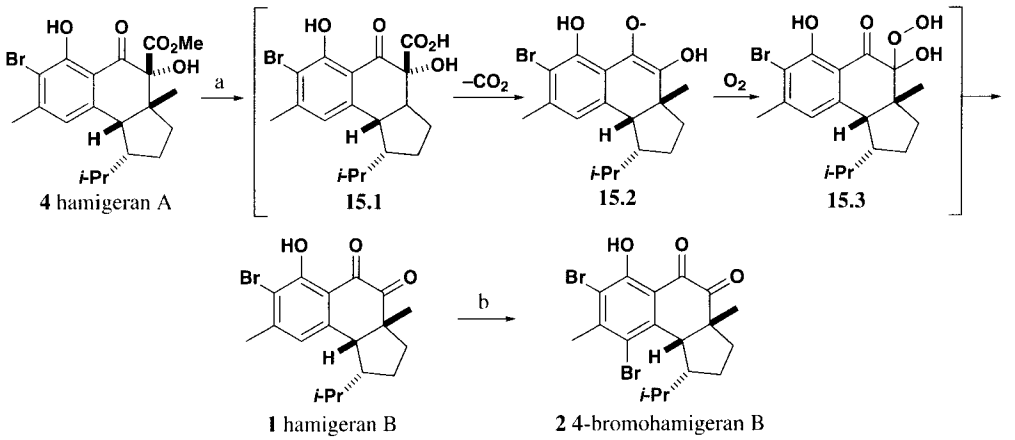
Reagents and conditions: a) BH_3OMe_2S, THF, sonication, 40°C, 68% (**14.1**:**14.2** ca 2:1); b) (i) PhOC(S)Cl, pyridine, 25°C; (ii) Bu_3SnH, AIBN, benzene, reflux, 64% for two steps; c) 1M HCl-THF, 80°C, 88%; d) PDC, 4Å molecular sieves, CH_2Cl_2, 83%; e) BBr_3, CH_2Cl_2, –78°C, 94%; f) NBS, *i*-Pr_2NH, CH_2Cl_2, 0°C, 95%

Scheme 14

23% yield. The compounds were separated chromatographically, and **14.1** was subjected to Barton-McCombie deoxygenation (**14.1** → **14.3**, 64%) *via* the phenylthionocarbonate. Acid hydrolysis released the expected diol **14.4** and PDC oxidation gave **14.5**. The curious observation was made that use of SO_3•pyridine-DMSO — a reagent employed with crude **12.1** — did not give *any* of the desired ketone. Presumably, if a different oxidant had been used in the earlier work (*cf. Scheme 12*), some material with the natural hamigeran stereochemistry might well have been isolated.

Demethylation of **14.5** with BBr_3 gave debromohamigeran A (**3**), and bromination with the NBS-*i*-Pr_2NH combination then produced hamigeran A (**4**).

In order to convert compounds of the hamigeran A series into those of the B series, a different and more efficient procedure from that used with racemic 5-*epi*-compounds (see *Scheme 7*) was devised. Treatment of **4** with $Ba(OH)_2$ in aqueous MeOH in the presence of air gave hamigeran B by the sequence: ester hydrolysis (**4** → **15.1**), decarboxylation (**15.1** → **15.2**), and auto-oxidation (**15.2** → **1**).[6c] Finally, bromination afforded synthetic 4-bromohamigeran B (**2**) (*Scheme 15*).



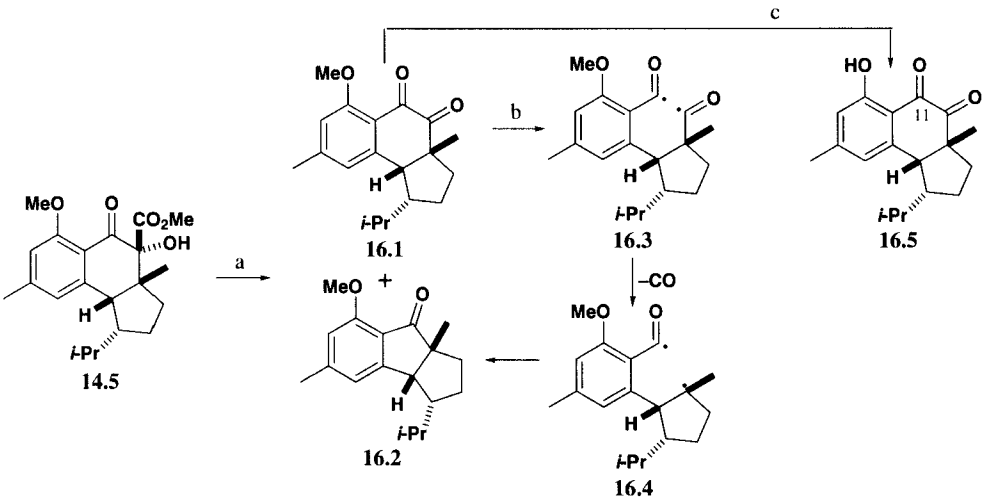
Reagents and conditions: a) $Ba(OH)_2$, MeOH-water, air, 87%; b) NBS, DMF; 94%

Scheme 15

The spectroscopic properties of compounds **1**-**4** matched the values reported for material of natural origin, and the specific rotations were also comparable; consequently, the originally assigned absolute configurations were confirmed.

During initial studies on the conversion of the C(O)-C(OH)CO_2Me unit into an α-diketone (*Scheme 16*, **14.5** → **16.1**), periodate cleavage was used, and an unexpected byproduct (**16.2**) was obtained.[6c] It was established that this material was produced by further reaction of the desired α-diketone and was, in fact, formed by a photochemical process (**16.1** → **16.3** → **16.4** → **16.2**, *Scheme 16*). Debromohamigeran B (**16.5**), obtained by demethylation (BBr_3) of

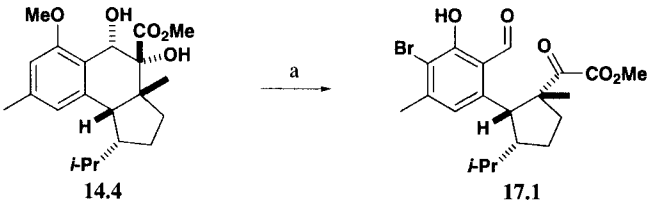
16.1, in which there is opportunity for hydrogen bonding between the phenolic hydroxyl and the C(11) carbonyl oxygen, does not undergo this photochemical ring contraction.



Reagents and conditions: a) KOH, then Bu_4NIO_4, heat; b) hν; c) BBr_3, CH_2Cl_2, –78°C, 86%

Scheme 16

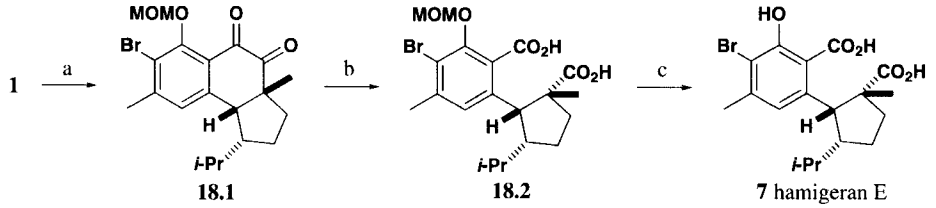
Treatment of diol **14.4** with MnO_2 (*Scheme 17*) gave keto aldehyde **17.1**; however, this substance was not taken further, although it could presumably have served as a precursor to other hamigerans.[6c]



Reagents and conditions: a) MnO_2, CH_2Cl_2, 90%

Scheme 17

With optically pure hamigeran B (**1**) in hand, it was then possible to gain access to its congener hamigeran E: the compound was protected as its MOM ether (**18.1**) and then subjected to oxidative cleavage under what appear to be carefully controlled conditions — H_2O_2, NaOH in a

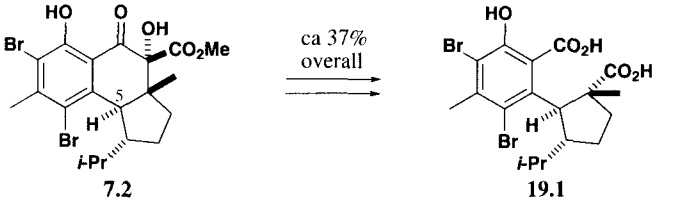


Reagents and conditions: a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 76%; b) 30% H_2O_2-dioxane-aq. NaOH, 0°C, 10 min, 70%; c) 3 M aq. HCl-THF, 25°C, 70%

Scheme 18

cold (0°C) aqueous biphasic mixture of water and dioxane for 10 min.[6c] The resulting dicarboxylic acid was treated with 3M hydrochloric acid to remove the MOM group, and chromatography over acid-washed silica gel gave hamigeran E (**7**) (50% from **18.1**).

The same sequence of reactions was used to convert racemic 5-*epi*-4-bromohamigeran B (**7.2**) into the corresponding isomer of hamigeran E (**19.1**) (*Scheme 19*).[6c]



7.2 **19.1**
(±)-5-epi-4-bromohamigeran E

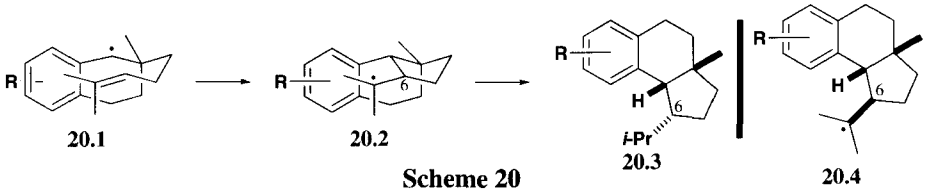
Scheme 19

In summary, the synthetic endeavors of Nicolaou, Gray and Tae resulted in the first conquest of the hamigerans as synthetic targets. Although the molecules are quite small by today's standards, it is clear that they pose a rather stern test.

II. SYNTHESIS OF HAMIGERAN B by Clive and Wang

The synthesis of hamigeran B by the authors of this review was the second report in this area; our work[8] was much more limited in scope than that of the Nicolaou group, as the purpose was to aim directly for hamigeran B — biologically, by far the most important member of the family.

A number of approaches were examined,[8c] but these early experiments did not lead very far. However, they gradually turned our attention to the possibility of radical cyclization along the lines of *Scheme 20*. Precedent for such a pathway could be inferred from the fact that radical



20.1 **20.2** **20.3** **20.4**

Scheme 20

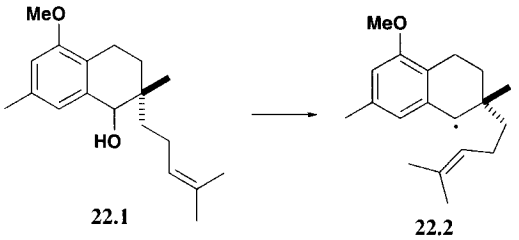
21.1 gives **21.2** with the methyl group on the *endo* face — an outcome that has been observed in a number of related cases.[9] It was appreciated, of course, that radical **20.1** includes a number of steric factors not present in **21.1**, but it was felt worthwhile to examine the possibility summarized

21.1 **21.2**

Scheme 21

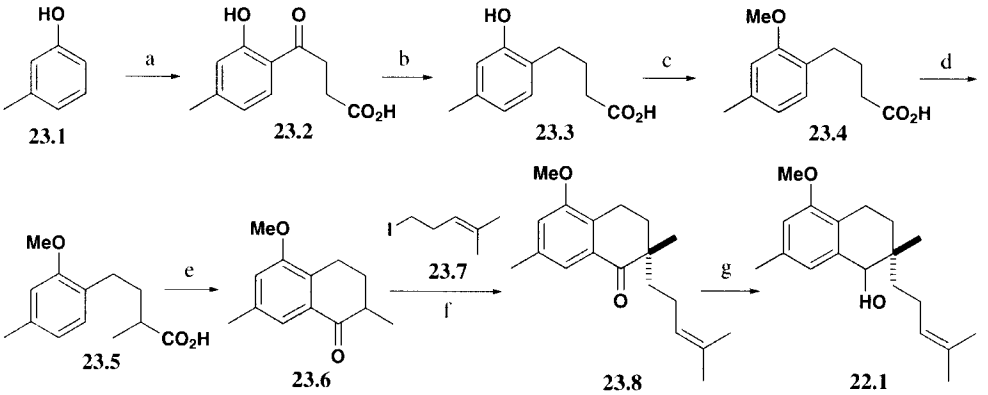
in *Scheme 20* (**20.1** → **20.3**). If successful, such a route would represent an impressive example of stereoelectronic effects in radical cyclization to solve an obviously difficult stereochemical problem. Secondly, it was expected that radical **20.1** would be a readily accessible species, so that putting this plan to the test would not involve much labor. In the event, all these speculations were misguided: radical **20.1** does not follow the desired pathway, but gives instead radical **20.4** with the unnatural stereochemistry for the isopropyl unit. Moreover, radicals of type **20.1** are by no means easy to generate; their precursors are difficult to assemble due to steric factors — the benzylic carbon is hindered because of the presence of the adjacent quaternary center and so acylation of appropriate benzylic alcohols is suppressed. The attempts to make radicals of type **20.2** led eventually to (±)-6-*epi*-hamigeran B, and the experience gained proved useful training for further work that gave the natural structure itself, first in racemic form, and shortly thereafter as the correct optically pure enantiomer.

The benzylic radical required to test the above proposal is **22.2** (*Scheme 22*). It was generated from alcohol **22.1** which, in turn, was prepared by the classical methods summarized



Scheme 22

in *Scheme 23*.[8c] The keto acid **23.2**[10] was made by subjecting *m*-cresol (**23.1**) to Friedel-Crafts acylation with succinic anhydride, and the unwanted ketone carbonyl was removed by Clemmensen reduction to produce **23.3**.[10] The phenolic hydroxyl was then methylated. All these



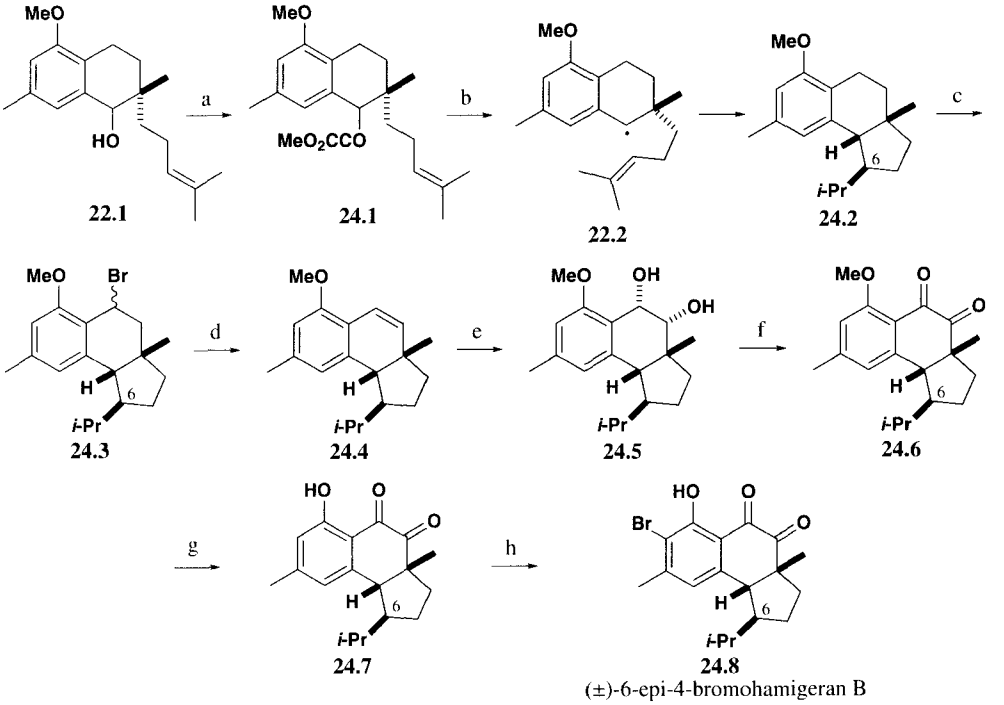
Reagents and conditions: a) succinic anhydride, $AlCl_3$; b) Zn, $HgCl_2$, HCl, heat; c) Me_2SO_4, NaOH, $Na_2S_2O_4$, 67% from **23.1**; d) LDA, THF, HMPA, MeI, –78°C to 0°C, 96%; e) $POCl_3$, $Cl_2CHCHCl_2$, heat, 83%; f) *t*-BuOK, PhMe, **23.7**, reflux, 80%; g) DIBAL-H, CH_2Cl_2, 0°C, 78%

Scheme 23

simple steps worked well, and **23.4** could be isolated in 67% yield overall from *m*-cresol. Methylation α to the carboxyl (**23.4** → **23.5**), using LDA, HMPA, and MeI was easily accomplished (96%), and intramolecular acylation, induced by treatment with $POCl_3$ in refluxing $Cl_2CHCHCl_2$, formed the tetralone **23.6**.[11] Alkylation in the standard way (LDA, THF) was not successful, but the ketone could be alkylated (80%) with iodide **23.7** using *t*-BuOK in PhMe.[12] Finally, DIBAL-H reduction gave a single alcohol (**22.1**), whose stereochemistry was not determined.

The hydroxyl group of **22.1** is hindered, and it did not react with 1,1'-thiocarbonyldiimidazole for the intended Barton-McCombie deoxygenation route to the required radical. Fortunately, reaction with MeOCOCOCl in the presence of pyridine did occur and was, in fact, very efficient (**22.1** → **24.1**, 93%), and set the stage for generating the crucial radical.[8c] Treatment of the mixed oxalate with Bu_3SnH and AIBN under standard conditions for radical cyclization gave **24.2** in high yield (89%). Preliminary NOE measurements suggested that the desired C(6) stereochemistry had indeed been generated, but this opinion had to be changed when, at a later stage, X-ray analysis of a derivative showed that the actual stereochemistry is as shown in **24.2**. In the meantime, the synthetic sequence was continued.

Benzylic bromination of **24.2** by irradiation in the presence of NBS gave **24.3**, which



(±)-6-epi-4-bromohamigeran B

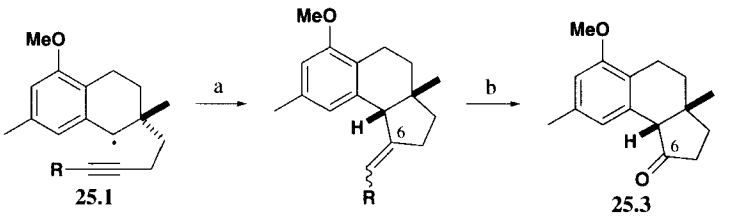
Reagents and conditions: a) MeO_2CCOCl, CH_2Cl_2, pyridine, 93%; b) Bu_3SnH, AIBN, PhH, reflux, 89%; c) NBS, CCl_4, Hanovia lamp; d) DBU, CCl_4, reflux; e) OsO_4, NMO, 56% from **24.2** (corrected for recovered **24.2**); f) Swern, 90%; g) $AlCl_3$, CH_2Cl_2, reflux, 78%; h) *i*-Pr_2NH, NBS, CH_2Cl_2, 0°C; 98%

Scheme 24

was presumed to be one or the other or both of the bromides represented by formula **24.3**, although, initially, we missassigned the stereochemistry at C(6). The material was too unstable to be purified, and was therefore treated directly with DBU to give **24.4** mixed with, and inseparable from, **24.2**. The crude mixture was subjected to standard conditions for vicinal dihydroxylation (catalytic OsO_4, NMO), after which diol **24.5** could be isolated in 56% overall yield from **24.2** (after correction for recovered **24.2**). Oxidation of the diol under Swern conditions proceeded in high yield (90%), and gave the crystalline diketone **24.6**. Single crystal X-ray analysis of the diketone revealed that the true — and disappointing — stereochemistry at C(6) was as shown. Compound **24.6** was obviously very close in structure to (±)-6-*epi*-hamigeran B (**24.8**), and so the route was taken to that stage.

The phenolic *O*-methyl group of **24.6** was removed by treatment with $AlCl_3$ (77%) — in our hands, use of BBr_3 was not successful (*cf. Scheme 13*) — and bromination at 0°C with NBS in the presence of *i*-Pr_2NH[7] gave (±)-6-*epi*-hamigeran B (**24.8**).

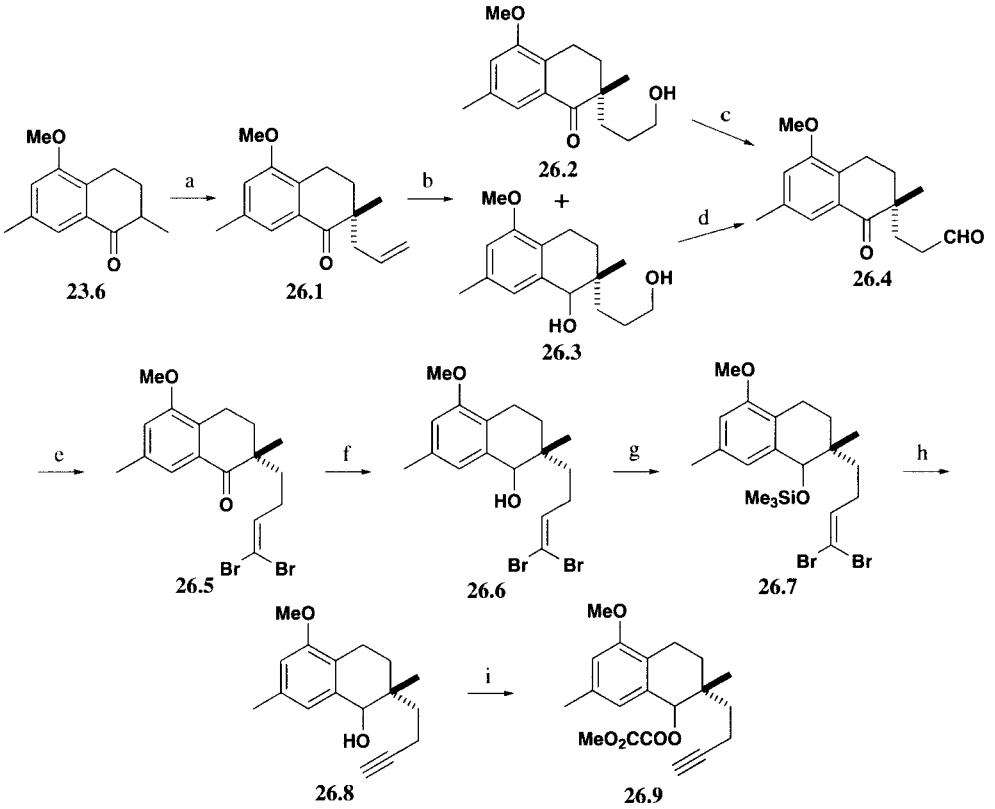
The outcome of the radical cyclization (**24.1** → **24.2**) obviously meant that a different method for dealing with the stereochemistry at C(6) had to be developed, and so the possibility was briefly examined of using radical cyclization onto a triple bond (*Scheme 25*). The expected product (**25.2**) should be cleavable to a ketone of type **25.3**. This ought to provide several opportunities for introducing an isopropyl group with the correct stereochemistry by Grignard addition, dehydration and hydrogenation — a sequence subsequently reported by the Nicolaou group.



Reagents and conditions: a) Bu_3SnH; b) O_3

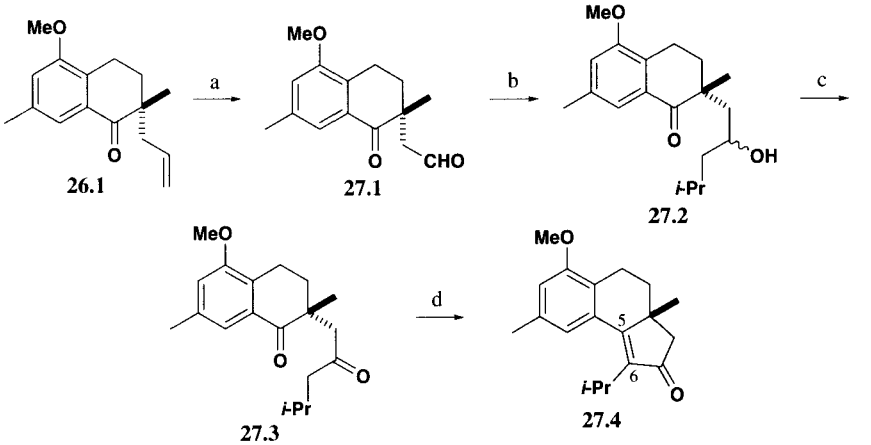
Scheme 25

Accordingly, ketone **23.6** was converted by standard methods (*Scheme 26*) into the mixed acetylenic oxalate **26.9**.[8c] Unfortunately, treatment with Bu_3SnH did not cause deoxygenation, and only hydrostannylation of the triple bond was observed. No attempt was made to suppress this hydrostannylation by replacing the acetylenic hydrogen by a large substituent; instead, radical cyclization routes were abandoned and a more classical — and, eventually, successful — approach was adopted. The initial plan (*Scheme 27*) was to hydrogenate enone **27.4** from the same face as the angular methyl group. It was appreciated that the tetrasubstituted nature of the double bond might make it difficult to hydrogenate;[13] moreover, inspection of Dreiding models suggested another potential difficulty, since it was not obvious from the shape of **27.4** whether hydrogenation would occur preferentially from the α or β face. However, appropriate conditions were indeed eventually found to saturate the C(5)-C(6) double bond in the desired manner.



Reagents and conditions: a) LDA, THF, allyl bromide, –78°C, 91%; b) 9-BBN, THF, 0°C; NaOH, H_2O_2, 20% yield of **26.2**, 70% yield of **26.3**; c) Dess-Martin periodinane, CH_2Cl_2, 65%; d) Swern oxidation, 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, pyridine, CH_2Cl_2, 80%

Scheme 26

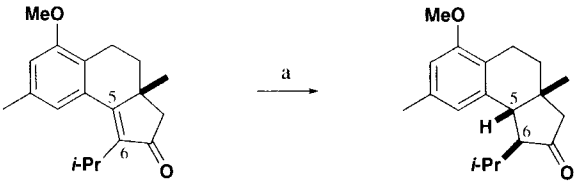


Reagents and conditions: a) OsO_4, $NaIO_4$, dioxane-water, 76%; b) *i*-BuMgCl, Et_2O, 89%; c) PCC, 87%; d) NaOH, EtOH-water, reflux, 98%

Scheme 27

Ketone **26.1** was converted by the Lemieux-Johnson method into aldehyde **27.1**, and then treatment with 1 equiv *i*-BuMgCl gave the expected epimeric alcohols **27.2**.[8c] These were oxidized (PCC) to generate diketone **27.3**. Finally, treatment with ethanolic NaOH produced the key intermediate **27.4** in almost quantitative yield, and the stage was set to tackle the problem of hydrogenating the C(5)-C(6) double bond.

Hydrogenation in MeOH over Pd-C (H_2, 48 psi) gave **28.1** as the major product (52%).[8c] Fortunately, the compound is crystalline, and X-ray analysis established the relative



27.4 **28.1**

Reagents and conditions: a) Pd-C, H_2, 48 psi, MeOH, 52%

Scheme 28

stereochemistry. As a working hypothesis, we assumed at the time that the desired C(6) stereochemistry had initially been generated, but that epimerization, mediated by the ketone carbonyl, then occurred. Accordingly, we decided to block this undesired pathway by reducing the ketone. Luche reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) of enone **27.4** was very slow, but reaction with DIBAL-H was rapid. However, the resulting alcohol is very acid-sensitive, and flash chromatography over silica gel caused elimination to occur, so that the compound actually isolated was the diene **29.1** (*Scheme 29*). On hydrogenation (MeOH, Pd-C, H_2, 52 psi) both double bonds of the diene

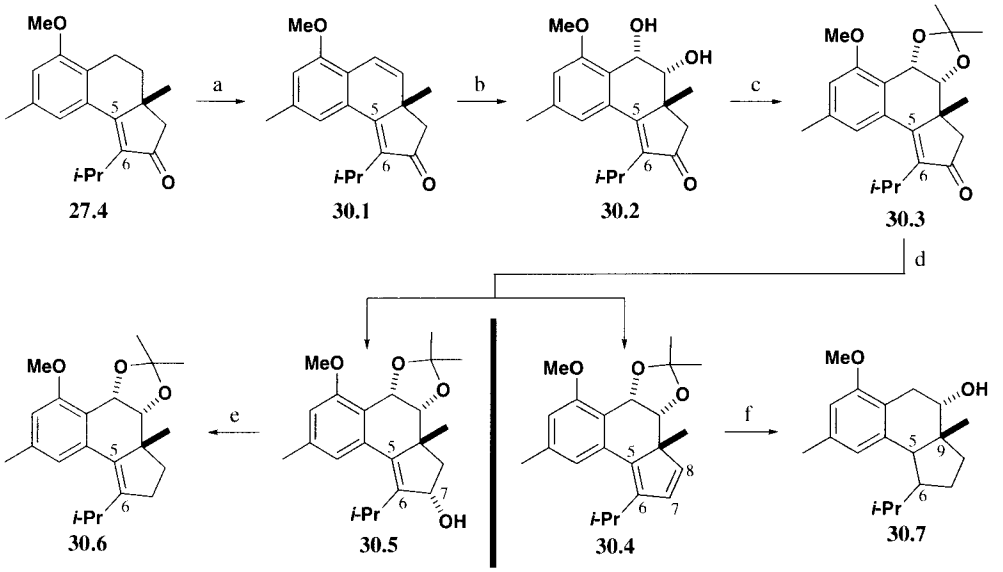
27.4 **29.1**

Reagents and conditions: a) DIBAL-H, silica, 98%

Scheme 29

system were saturated, but the product was a mixture of stereoisomers, with the ratio of the components varying from experiment to experiment. At the time, we attributed this outcome to a lack of facial selectivity, and so we decided to place a bulky substituent on the α face of **27.4**.

To this end, ketone **27.4** was dehydrogenated with DDQ (*Scheme 30*)[8c] and subjected to dihydroxylation. The stereochemical outcome was controlled by the angular methyl group, which caused reaction to occur on the α face, as desired. The resulting diol (**30.2**) was then converted into the corresponding ketal **30.3** in the hope that the heterocyclic subunit would direct the subsequent hydrogenation to the opposite face.



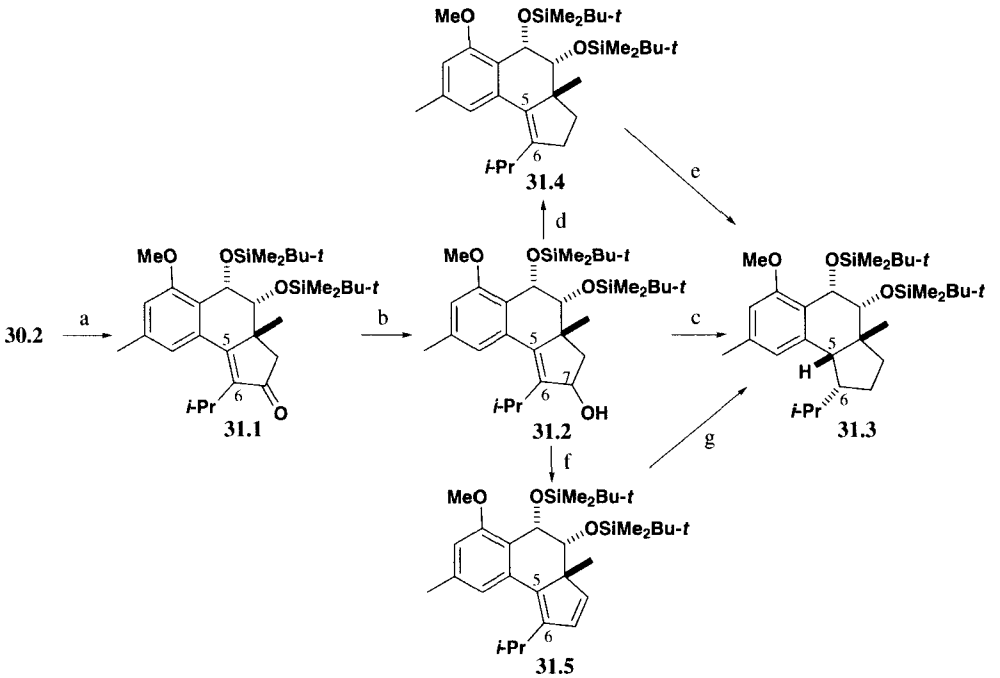
Reagents and conditions: a) DDQ, dioxane, reflux, 78%; b) OsO_4, NMO, 98%; c) $Me_2C(OMe)_2$, pyridinium *p*-toluenesulfonate, acetone, 88%; d) DIBAL-H, CH_2Cl_2, 0°C, 54% yield of **30.5**, 23% yield of **30.4**; e) Pd-C, H_2, 33 psi, MeOH, 80%; f) Pd-C, H_2, 35 psi, MeOH, 92%

Scheme 30

The carbonyl group of **30.3** was reduced with DIBAL-H to give a 1:2.3 mixture of diene **30.4** and allylic alcohol **30.5** [whose stereochemistry at C(7) was not firmly established]. Hydrogenation of **30.5** (MeOH, Pd-C, H_2, 33 psi) for 1 h gave olefin **30.6** in high yield (80%), but use of longer reaction times resulted in hydrogenolysis of the C(11)-O benzylic bond — at least as judged by the absence of ^{1}H NMR signals at ca δ 5 for the benzylic CH-O.

Hydrogenation (MeOH, Pd-C, H_2, 35 psi) of diene **30.4** for 36 h led to **30.7** (of unestablished stereochemistry). With other catalysts [Rh-Al_2O_3, 700 psi, 50°C, MeOH, 19 h; Wilkinson's catalyst (400 psi, 50°C, MeOH, 48 h); Raney nickel 2800 (1150 psi, 60°C, MeOH, 67 h] only the C(7)-C(8) double bond of **30.4** was saturated. The mono olefin **30.6** did not react with BH_3 or 9-BBN in refluxing THF.

The finding that hydrogenolysis of the benzylic oxygen of **30.4** occurred suggested a further modification to the route. In order to avoid the hydrogenolysis, we decided to protect the hydroxyl groups of **30.2** with protecting groups having sufficient bulk to suppress coordination of the benzylic oxygen to the catalyst. We suspected that *tert*-butyldimethylsilyl groups would be suitable in this respect, and so the diol was treated with *t*-$BuMe_2SiOSO_2CF_3$ in the presence of 2,6-lutidine (*Scheme 31*)[8c] to produce **31.1**. DIBAL-H reduction gave alcohol **31.2** [stereochemistry at C(7) not established], and hydrogenation (Pd-C, MeOH, 50 psi, 36 h) did indeed give the desired stereochemical outcome, but the product (**31.3**) was obtained in only 18% yield. With a shorter reaction time (6.5 h) hydrogenolysis of the allylic hydroxyl occurred, and mono-olefin

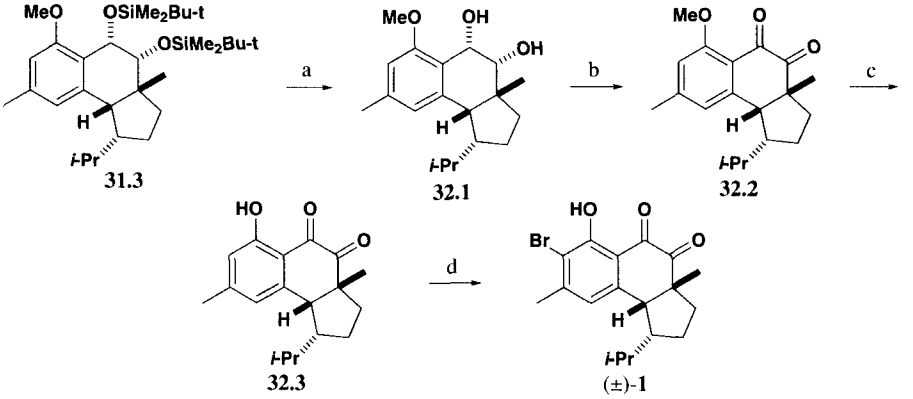


Reagents and conditions: a) *t*-BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 84%; b) DIBAL-H, CH_2Cl_2, 0°C, 94%; c) Pd-C, H_2, 50 psi, MeOH, 36 h, 18%; d) Pd-C, H_2, 56 psi, MeOH, 6.5 h, 35%; e) Pd-C, H_2, 50 psi, MeOH, 36 h, 93%; f) MsCl, Et_3N, $ClCH_2CH_2Cl$, reflux, 80%; g) Pd-C, H_2, 39 psi, MeOH-hexane, 36 h, 85%

Scheme 31

31.4 was produced (35%). However, prolonged hydrogenation of this compound gave the desired product (**31.3**) in 93% yield. It appeared that the hydroxyl group of **31.2** has a deleterious effect on the course of the hydrogenation, and so we dehydrated **31.2** to diene **31.5** by mesylation and thermolysis in the presence of an excess of Et_3N. Hydrogenation of **31.5** now proceeded exactly according to plan (Pd-C, MeOH, H_2, 39 psi) to giving **31.3** in 85% yield.

Desilylation with Bu_4NF was almost quantitative (*Scheme 32*, **31.3** → **32.1**),[8c] and the

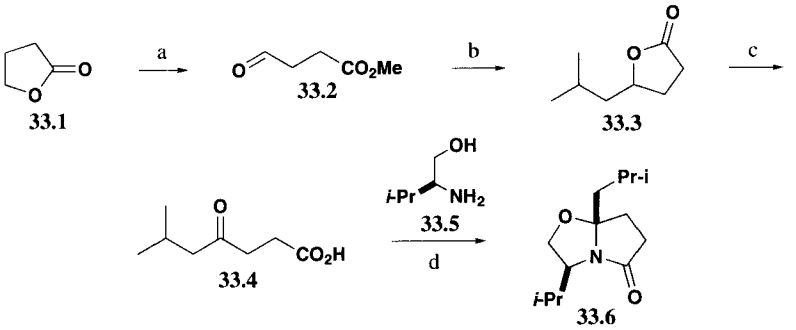


Reagents and conditions: a) Bu_4NF, 98%; b) Swern, 92%; c) LiCl, DMF, 78%; d) NBS, *i*-Pr_2NH, 94%

Scheme 32

resulting diol was subjected to X-ray analysis to confirm the stereochemical assignment. Swern oxidation served to convert the diol into an α-diketone (**32.1** → **32.2**), and there remained only the deprotection of the phenolic oxygen and introduction of bromine. The first of these tasks was initially troublesome, as use of BBr_3 or Me_3SiI was unsuccessful, but with LiCl in hot DMF, phenol **32.3** was isolated in 75% yield. Finally, bromination[7] with NBS in the presence of *i*-Pr_2NH at 0°C gave hamigeran B (**1**) (94%).

A special characteristic of the above route is that an asymmetric synthesis depends only on the construction in optically pure form of the quaternary center, as the other two asymmetric centers are controlled by that feature. In the synthesis of racemic hamigeran B the key asymmetric intermediate is enone **27.4**, and so we sought a route by which it might be made in enantiomerically pure form. The essential feature in this regard is the asymmetric quaternary carbon,[14] and Meyers's method[15] was obviously the one that should be tried first; the required substrates would be the lactam **33.6** and the iodide **34.4**. The former was made by the obvious route summarized in *Scheme 33*.[8c] γ-Butyrolactone (**33.1**) was converted into the aldehyde ester



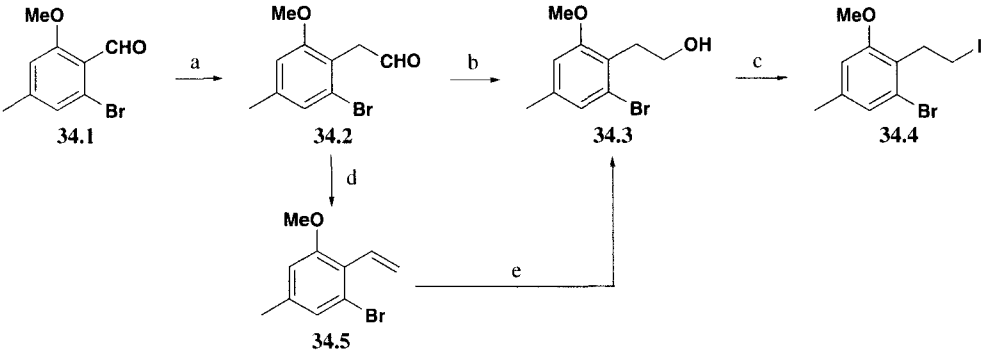
Reagents and conditions: a) MeOH, H_2SO_4, then PCC, 73%; b) *i*-BuMgCl, Et_2O; c) AcOH, H_2SO_4, Na_2CrO_7, 53% from **61**; d) PhMe, reflux, Dean-Stark apparatus, 75%

Scheme 33

33.2 by methanolysis and PCC oxidation. Treatment of **33.2** with 1 equiv *i*-BuMgCl directly gave lactone **33.3**, and oxidation with $Na_2Cr_2O_7$ in a mixture of AcOH and H_2SO_4 generated keto acid **33.4** in 53% overall yield from the aldehyde ester **33.2**. The required lactam (**33.6**) was then made in the standard way[16] by condensation with (*S*)-valinol.

The other subunit, iodide **34.4** was accessible from the known bromide **34.1** which happened to be available in this laboratory from synthetic work related to puraquinonic acid.[17]

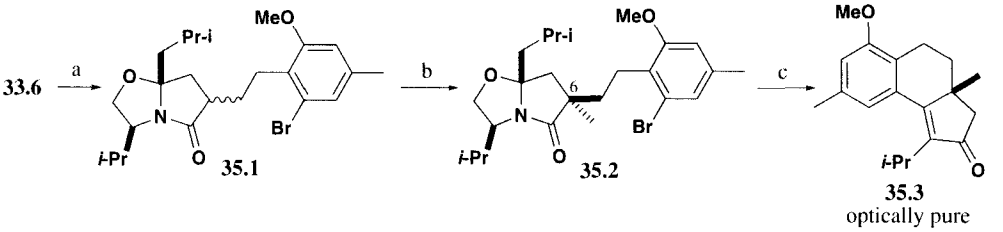
Homologation of **34.1** by Wittig reaction with the ylide generated from $MeOCH_2PPh_3Br$, and acid hydrolysis of the resulting enol ethers gave aldehyde **34.2**.[8c] The desired iodide **34.4** was then prepared by reduction (DIBAL-H) and replacement of the hydroxyl by iodine. The same compound was also available by Wittig olefination to **34.5** (**34.2** → **34.5**), which was then converted into alcohol **34.3** by hydroboration.



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%

Scheme 34

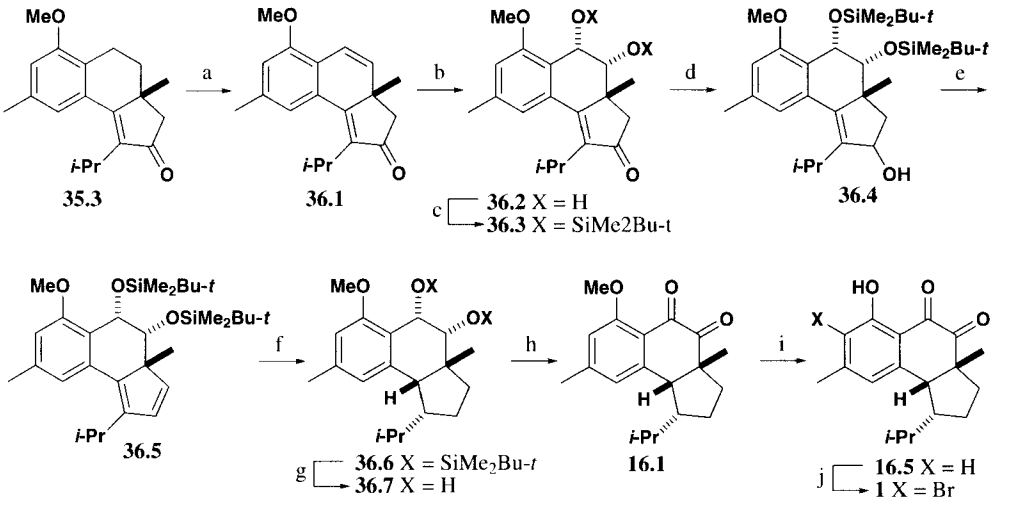
Lactam **33.6** was alkylated (*Scheme 35*)[8c] with the iodide by deprotonation of the former with LDA (1.5 equiv at –78°C), followed by addition of HMPA and then the iodide. After a prolonged reaction time at room temperature (36 h), the coupled product **35.1** could be isolated



Reagents and conditions: a) LDA (1.5 equiv), THF, HMPA, **34.4**, –78°C, 79% corrected for recovered **33.6**; b) LDA, THF, HMPA, MeI, –78°C, 90%; c) (i) *t*-BuLi, THF, –78°C; (ii) 1M aqueous $Bu_4NH_2PO_4$, reflux; (iii) NaOH, EtOH-water, reflux, 90%

Scheme 35

in acceptable yield [79%, after correction for recovered lactam (30%)]. Repetition of the alkylation, but this time with MeI, gave an 18:1 mixture of the required lactam **35.2** and its C(6) epimer. Fortunately, the compounds were easily separated. Treatment of **35.2** with *t*-BuLi at –78°C, followed by refluxing with an aqueous solution of 1M $Bu_4NH_2PO_4$ for 24 h, and then with ethanolic NaOH induced[15a] the expected cascade of reactions, ultimately affording **35.3** in 90% overall yield from **33.6**. From its method of synthesis, enone **35.3** was optically pure and, at this point, the sequence already worked out in the racemic series was applied. The enone was first desaturated and dihydroxylated (*Scheme 36*, **35.3** → **36.1** → **36.2**).[8c] Silylation, DIBAL-H reduction, and mesylation again gave a diene (**36.5**), and both double bonds were then hydrogenated, taking the route as far as **36.6**. Removal of the silicon protecting groups released the diol **36.7**, which we judged to be optically pure by HPLC analysis on a chiral column. Swern oxidation, demethylation, and regioselective bromination finally gave (–)-hamigeran B (**1**).



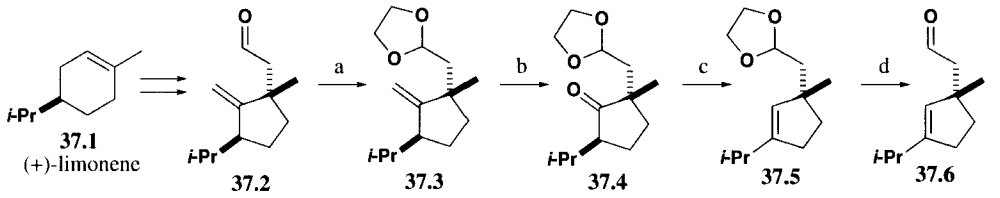
Reagents and conditions: a) DDQ, dioxane, reflux, 74%; b) OsO_4, NMO, 81%; c) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0°C, 73%; d) DIBAL-H, CH_2Cl_2, 0°C; e) MsCl, Et_3N, $ClCH_2CH_2Cl$, 25°C then reflux, 84% from **36.3**; f) Pd-C, H_2, 39 psi, MeOH-hexane, 78%; g) Bu_4NF, THF, reflux, 85%; h) Swern oxidation, 94%; i) LiCl, DMF, reflux, 87%; j) NBS, *i*-Pr_2NH, CH_2Cl_2, 0°C, 88%

Scheme 36

This synthesis uses rather simple reactions and should be amenable to scale-up. Although we initially used purely steric arguments to justify the choice of silicon protecting groups to suppress hydrogenolysis of a benzylic C-O bond, a later search of the literature revealed that hydrogenolysis is believed to involve development of a partial positive charge on the benzylic carbon.[18] Siloxy groups have a lowered ability to stabilize an adjacent positive charge,[19] and so the effect we have observed may also result from electronic factors. Several examples are known in which a benzylic silyl ether survives hydrogenation of di-,[20] tri-,[6c] and tetrasubstituted[21] double bonds, but the publications reporting these experiments make no comment on the possible role of the silicon protecting group in suppressing hydrogenolysis.

III. SYNTHESIS OF (–)-6-*EPI*-HAMIGERAN B by Mehta and Shinde

The Mehta group has examined the possibility of making hamigeran B from material in the chiral pool.[22] Earlier work in Mehta's laboratory had involved the conversion of the readily-available monoterpene *R*-(+)-limonene (**37.1**) into the cyclopentyl aldehyde **37.2**. This proved to be a useful building block for terpene synthesis,[23] and was selected in the present case. First of all, a number of standard operations were used to convert **37.2** into the olefinic aldehyde **37.6**, which was intended — as suggested by the orientation in which the structure has been drawn — to represent the right-hand portion of hamigeran B.[22] Protection of the aldehyde group of **37.2** as an acetal was effected in high yield (95%) using *bis*(trimethylsiloxy)ethane. Ozonolytic cleavage of the double bond (**37.3** → **37.4**) and borohydride reduction gave an alcohol[24] which was dehydrated

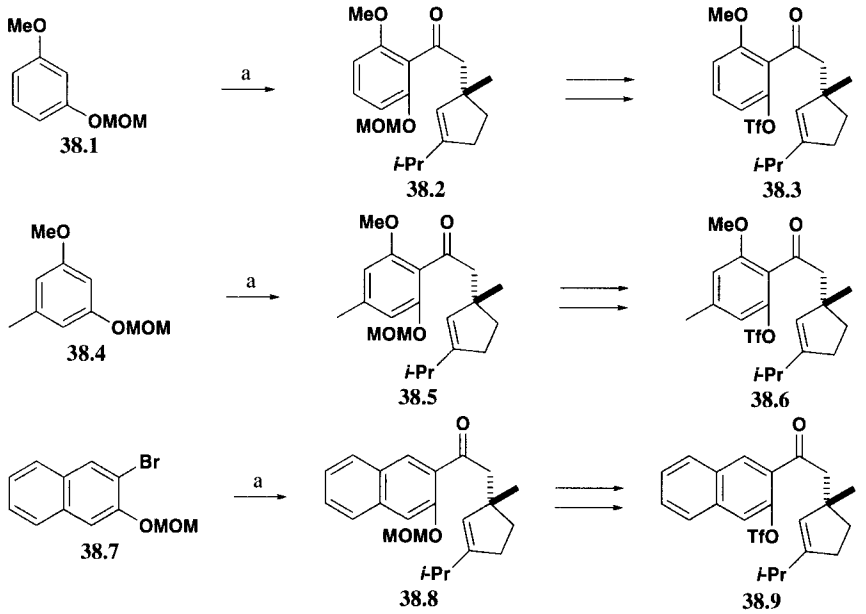


Reagents and conditions: a) $Me_3SiOCH_2CH_2OSiMe_3$, Me_3SiOTf, CH_2Cl_2, –78°C, 95%; b) O_3, MeOH, –78°C, Me_2S, –78°C, 60%; c) (i) $NaBH_4$, MeOH, 0°C, 95%; (ii) $POCl_3$, pyridine, 0°C, 50%; d) HCl, THF, 70%

Scheme 37

under classical conditions ($POCl_3$, pyridine) to introduce a double bond (**37.4** → **37.5**) that was needed later to serve as a point of attachment to the left-hand aromatic ring by means of an intramolecular Heck coupling. To this end, the aldehyde was liberated from its acetal, so that the aromatic ring could be attached by carbonyl addition of an aryl organolithium.

A potential advantage of the Mehta approach, in which the target is to be assembled from two units, is that it provides good opportunities to make a number of analogs that have variations in the aromatic segment, and to do so without redesigning the synthetic plan. In the event, three different aryllithiums (*Scheme 38*), each generated by directed lithiation, were added to

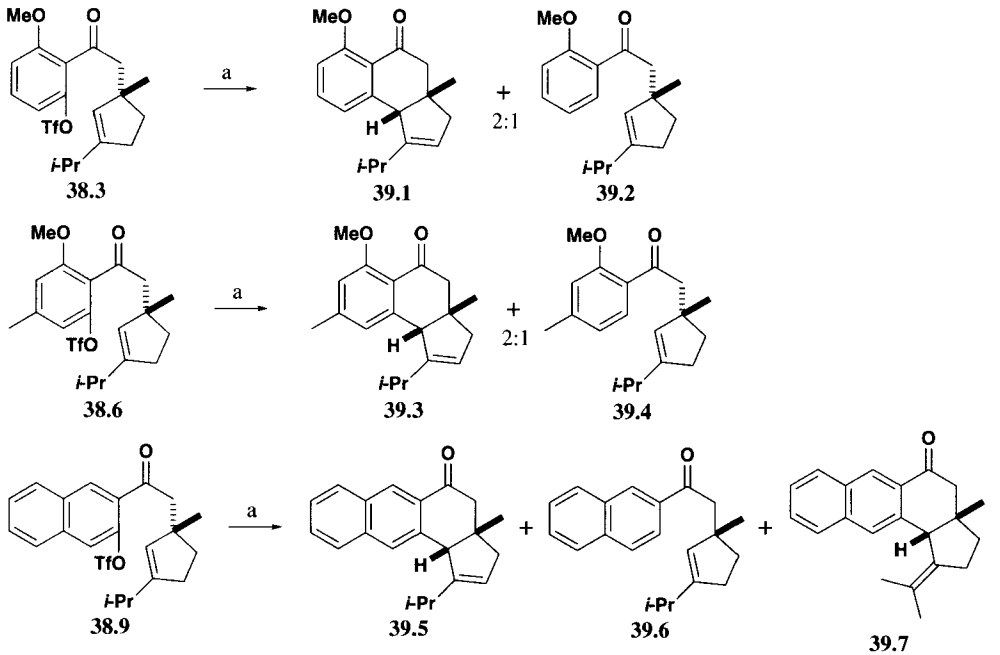


Reagents and conditions: a) *t*-BuLi, 0°C, 1 h, then **37.6**, –78°C to 0°C, then PDC, 4Å sieves, 40% overall

Scheme 38

aldehyde **37.6**, and the resulting alcohols[25] were oxidized with PDC to the expected ketones (**38.2**, **38.5**, **38.8**). In each case, the MOM-protected phenolic hydroxyl in the product was released by acid hydrolysis (ca 80%), and converted equally efficiently into the corresponding

triflate, so as to set the stage for Heck cyclization. Of the three triflates prepared, only **38.6** is suitable for the intended elaboration into hamigeran B, but each triflate was subjected to Heck cyclization (*Scheme 39*). It was appreciated that the sterically hindered nature of the olefinic

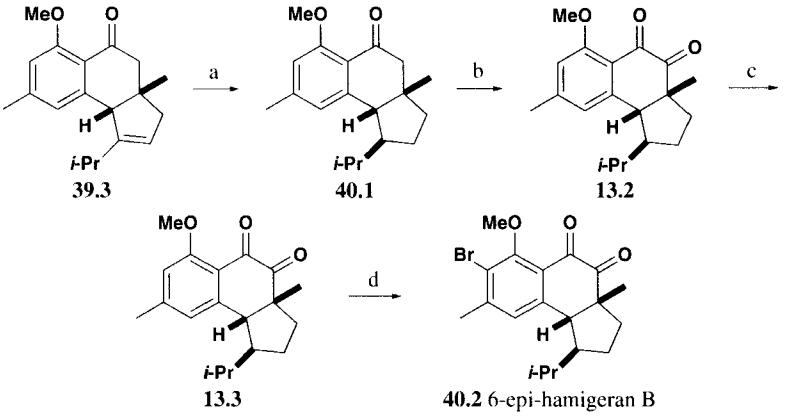


Reagents and conditions: a) $Pd(OAc)_2$, 1,3-*bis*(diphenylphosphino)propane, Et_3N, DMF, 90°C, 55-60%

Scheme 39

double bond might hinder the cyclization but, it was eventually found that use of 20 mol% of $Pd(OAc)_2$, a corresponding amount of 1,3-*bis*(diphenylphosphino)propane and some Et_3N at 90°C in DMF effected the required bond formation, and ring-closed products could be isolated in 55-60% yield.[26] This result was satisfactory, but the Heck reaction was not straightforward: both **38.3** and **38.6** gave the endocyclic olefins **39.1** and **39.3**, respectively, but the naphthalene derivative **38.9** afforded two cyclized olefins with the exocyclic isomer **39.7** predominating. In all cases, significant amounts of non-cyclized, but reduced, material, arising by replacement of the CF_3SO_3 group by hydrogen was isolated, the ratio of cyclized to uncyclized products being 2:1 in the first two cases and 3:1 in the naphthalene example. The *cis* ring fusion stereochemistry is expected on mechanistic grounds, and was later confirmed for the critical example **39.3**, which has the appropriate substitution pattern for the planned elaboration into hamigeran B.

Catalytic hydrogenation of **39.3** (*Scheme 40*) gave a crystalline substance in quantitative yield, shown by X-ray analysis to have the structure and stereochemistry defined by **40.1**. While the X-ray results confirmed the ring fusion stereochemistry expected for **39.3**, they revealed the unwelcome fact that hydrogenation had occurred from the more hindered concave face, because the isopropyl group had the unnatural configuration. Attempts to obtain the desired



39.3 **40.1** **13.2**

13.3 **40.2** 6-epi-hamigeran B

Reagents and conditions: a) Pd-C, H_2, 100%; b) SeO_2, AcOH, dioxane-water, reflux, 80%; c) BBr_3, CH_2Cl_2, –20°C, 90%; d) NBS, *i*-Pr_2NH, CH_2Cl_2, 90%

Scheme 40

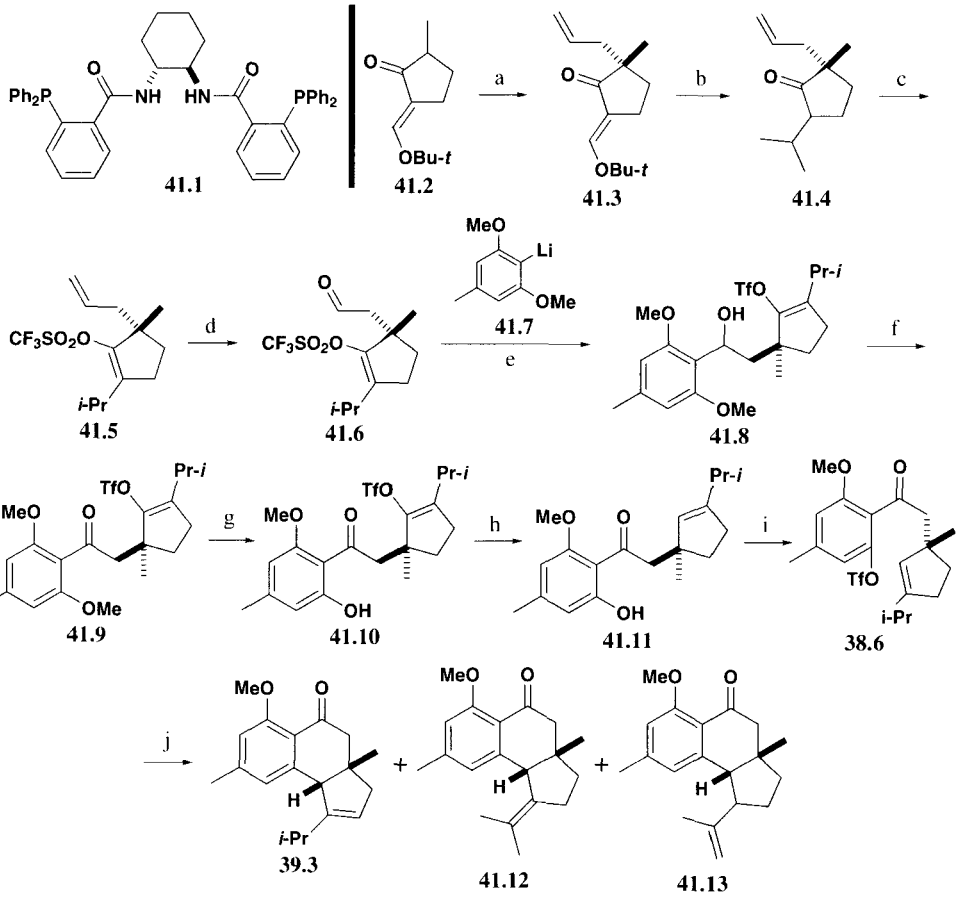
isomer by changes in catalyst and solvent were unsuccessful, and so (–)-6-*epi*-hamigeran B, which was now within easy reach, was accepted as a new target.

The required second carbonyl was introduced by reaction of **40.1** with SeO_2, and the *O*-methyl group was removed by the action of BBr_3 at –20°C (90%). Finally, bromination in the presence of *i*-Pr_2NH, afforded (–)-6-*epi*-hamigeran B (**40.2**). This route should be capable of affording a variety of 6-*epi*-hamigerans.

IV. SYNTHESIS OF HAMIGERAN B by Trost, Pissot-Soldermann, Chen, and Schroeder

The synthetic work reported by the Trost group,[27] like that or Mehta and Shinde, relies on the optically active intermediate **38.6**, which was subjected to intramolecular Heck cyclization (*Scheme 41*, **38.6** → **39.3**) under slightly different conditions from those used by Mehta and Shinde, but with what appear to be comparable results.

While Mehta and Shinde used starting material from the chiral pool to set the absolute stereochemistry of the quaternary center, Trost and his collaborators applied the palladium-catalyzed asymmetric allylic alkylation developed in his group to deal with construction of the quaternary center in the correct absolute configuration. In the event, the first intermediate having that feature was obtained in good yield and with an ee of 95%, providing an impressive example of the allylation methodology. With **39.3** in hand, the Trost group performed the stereochemically crucial hydrogenation step under different conditions from those examined by Mehta and Shinde, and were rewarded with a stereochemical outcome that was exactly the required one. A comparison of the corresponding hydrogenation steps in the two routes provides a clear example of the highly empirical nature of complex molecule synthesis and the fact that seemingly minor changes in substrate or reaction conditions can lead to significantly different results.



Reagents and conditions: a) LDA, allyl acetate, Me_3SnCl, $[\eta^3\text{-}C_3H_5PdCl]_2$, **41.1**, 77%, 93% ee; b) Me_2CuLi, Et_2O, –20°C to r. t., 89%; c) LDA, $PhN(SO_2CF_3)_2$, THF, 0°C to r. t., 87%; d) OsO_4, NMO, then $NaIO_4$; e) **41.7**, DME, –55°C; f) Dess-Martin periodinane, $NaHCO_3$, 75% from **41.5**; g) BCl_3, CH_2Cl_2, –20°C, 86%; h) $Pd(OAc)_2$, 1,1'-*bis*(diphenylphosphino)ferrocene, HCO_2H, Et_3N, DMF, 70°C, 94%; i) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0°C to room temperature, 94%; j) $Pd(OAc)_2$, *bis*(diphenylphosphino)butane, K_2CO_3, PhMe, 107°C, 58% yield of **39.3**

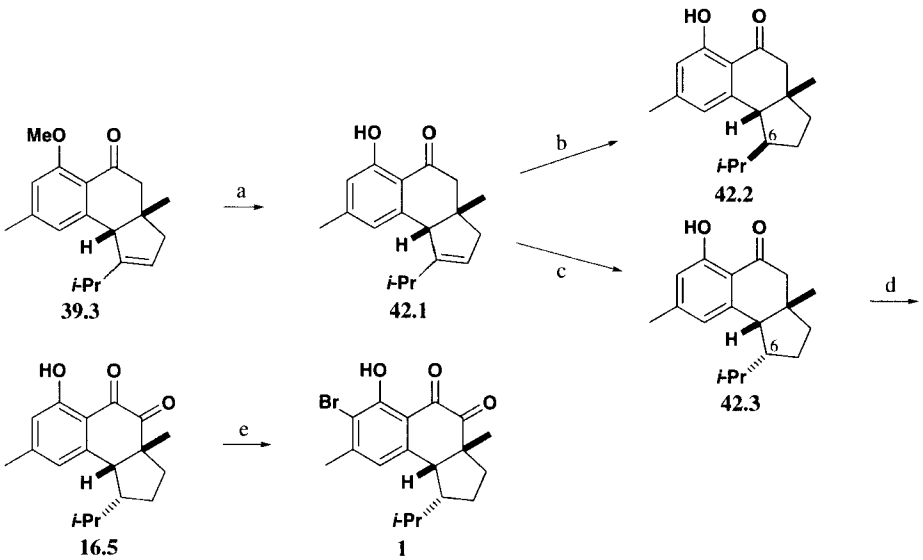
Scheme 41

The known cyclopentanone **41.2** was allylated[27] (**41.2** → **41.3**) with allyl acetate under conditions previously developed with other ketones. The procedure involved use of the chiral catalyst **41.1** and $[\eta^3C_3H_5PdCl_2]$ in the presence of LDA, Me_3SiCl and *t*-BuOH. The need for the alcohol was a serendipitous discovery: initial experiments gave high ee's, while later ones, in which a new bottle of BuLi was used, gave poor results, and it was quickly suspected that lithium alkoxide impurities in the original (and old) bottle of BuLi might have been responsible for the early satisfactory results. This suspicion was quickly verified, and optimization studies showed that use of 7 equiv of *t*-BuOH was ideal. Use of only 1 mol% of Pd catalyst and only 2 mol% of the ligand saw a further increase in ee. The allylation process was actually developed

with the enantiomer of **41.1** (giving the enantiomer of **41.3**) but has been described here as though the correct (for hamigeran B) enantiomer had been used. It was suggested[27] that the presence of *t*-BuOLi influences the nature of the enolate cluster.

The alkoxymethylene group of **41.3** was converted directly into an isopropyl group (**41.3** → **41.4**) by treatment with Me_2CuLi, and the intermediate ketone was then converted into triflate **41.5** under standard conditions [LDA, $PhN(SO_2CF_3)_2$]. Oxidative cleavage of the pendant double bond (OsO_4, NMO, $NaIO_4$) gave aldehyde **41.6**, ready for attachment of the left-hand aromatic unit. Reaction with lithiated dimethyl orcinol (**41.7**), and oxidation (Dess-Martin) afforded the expected ketone **41.9**. One methoxy group was next demethylated with BCl_3 (**41.9** → **41.10**), the triflate was subjected to palladium-mediated reduction by formic acid (**41.10** → **41.11**), and the phenolic hydroxyl in the product of these operations was converted into a triflate (**41.11** → **38.6**). At this point, Heck reaction, under slightly different conditions from those used by Mehta and Shinde, gave a mixture of three alkenes: **39.3**, **41.12**, and **41.13**. The potential problem of hydrogenolysis of the triflate (observed in the procedure of Mehta and Shinde) was suppressed by using K_2CO_3 instead of Et_3N. Under optimized conditions [*bis*(diphenylphosphino)butane as ligand], **39.3** was isolated in 58% yield. Formation of **41.12** and **41.3** was not observed by Mehta and Shinde (who used Et_3N).

With **39.3** in hand, the stage for the critical hydrogenation had been reached but, as a preliminary, the phenolic oxygen was released from its methyl ether by treatment with BBr_3 in order to avoid reduction of the carbonyl group, although Mehta's observations (published after the present work was done) suggest that this was an unnecessary precaution. Hydrogenation over



Reagents and conditions: a) BBr_3, 51% from **38.6**; b) Pd-C, H_2, 62%; c) Ir black, H_2, 100%; d) SeO_2, AcOH, dioxane, 90%; e) NBS, *i*-Pr_2NH, 85%

Scheme 42

Pd-C in EtOH (1500 psi) gave exclusively the undesired 6-*epi*-product **42.2**. Reasoning that an epimerization at C(6) may have occurred because of a slow final reductive elimination, thereby allowing olefin isomerization to occur, the Trost group then examined use of iridium, which is known[28] to minimize such isomerization. With iridium black, only the desired isomer **42.3** was formed (100%). The material had an ee of 93% and its structure was confirmed by X-ray analysis. Oxidation with SeO_2 (**42.3** → **16.5**) and bromination (NBS, catalytic *i*-Pr_2NH) at 0°C gave (–)-hamigeran B (**1**), presumably of 93% ee or greater.

The utility of the Trost asymmetric alkylation methodology and the mechanistic insight into the initial undesired hydrogenation results, leading to the use of iridium, are particularly noteworthy.

V. SYNTHESIS OF (±)-HAMIGERAN B by Piers and Lau

Piers and Lau have reported[29] a concise synthesis of (±)-hamigeran B and (±)-4-bromo-hamigeran B at an ACS meeting, although details of the route have not yet been published.

Acknowledgements.- We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

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(Received October 26, 2004; in final form January 5, 2005)