A Short and Concise Asymmetric Synthesis of Hamigeran B

Barry M. Trost,* Carole Pissot-Soldermann, and Irwin Chen[a]

Abstract: The interesting biological properties of the hamigerans wherein hamigeran B is a potent antiviral agent with low cytotoxicity to host cells make these deceptively simple looking structures challenging synthetic targets. A strategy to hamigeran B evolved wherein the three contiguous stereocenters are established ultimately from a Pd catalyzed asymmetric allylic alkylation (AAA). The latter involves an asymmetric allylation of a non-stabilized ketone enolate in 77% yield and 93% *ee*. By using this process, (*S*)-5-allyl-2-isopropyl-5-methyl-1-trifluoromethanesulfonyloxycyclopentene becomes available in four steps from 2-methylcyclopentanone. Introduction of the aryl unit by cross-coupling proceeded intermolecularly but failed intramolecularly. On the other hand, reductive removal of the triflate permitted a Heck reaction to effect intramolecular introduction of the aryl ring. The unusual conformational properties of this molecular architecture are revealed by the regioselectivity of the β-hydrogen elimination in the Heck reaction and the diastereoselectivity of the reduction establishing the stereochemistry of the carbon bearing the isopropyl group. The successful route consists of 15 steps from 2-methylcyclopentanone and dimethylorcinol illustrating the efficiency of the route based upon the Pd AAA.

Keywords: alkylation · asymmetric catalysis · Heck reaction · palladium · total synthesis

Introduction

The hamigerans are a novel bioactive family of metabolites isolated from the poecilosclerid sponge *Hamigera tarangaensis* Berquist and Fromont (family Anginoidae, syn. Phorbasidae) from the Hen and Chicken Islands off the coast of New Zealand.[1] These natural products contain a unique carbon skeleton in which a substituted aromatic nucleus is fused onto a [4.3.0] or [5.3.0] carbocyclic core that contains three or four contiguous stereogenic centers one of which features an isopropyl group (Figure 1). The biological evaluation of these compounds ranges from moderate in vitro antitumor activity against P-388 leukemia cells (hamigeran D) to pronounced antiviral activity. Indeed, hamigeran B showed 100% virus inhibition against both the herpes and polio viruses, with only slight cytotoxicity throughout the host cells.

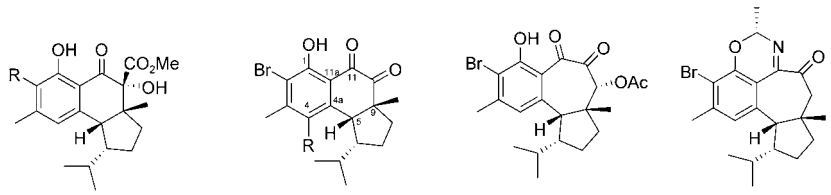

Figure 1. Structure of hamigerans.

Despite the relatively small size, the hamigerans offer both a challenge and an opportunity to apply new synthetic tools developed in our laboratories. Moreover, the structural features of hamigerans and the recent development of the palladium catalyzed asymmetric allylic alkylation (AAA) of ketone enolates[2] prompted us to devise a straightforward route to this family. We chose hamigeran B as our target due to its pronounced antiviral activity. In this paper, we delineate our study culminating in a concise convergent synthesis of hamigeran B.

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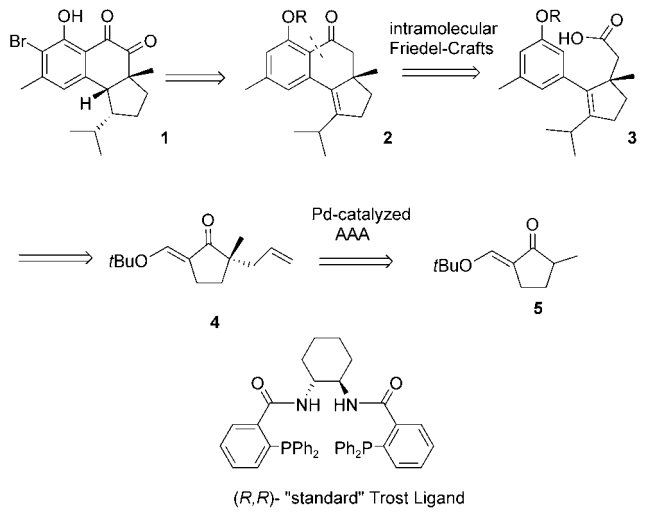
Results and Discussion

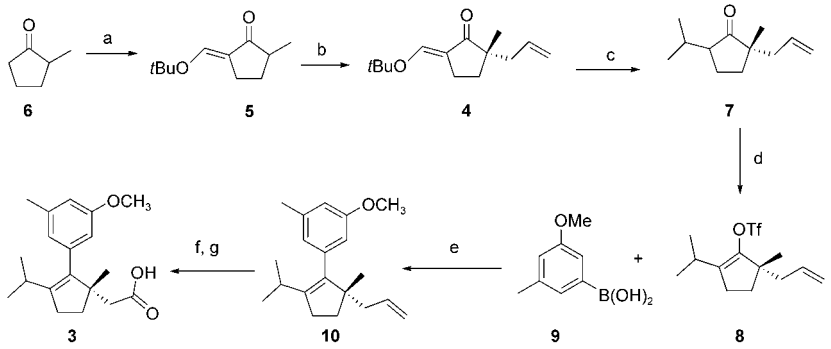
Initial forays: Our interest stemmed from the question of whether setting the stereochemistry of the quaternary center from which all the remaining stereocenters may evolve might be achievable by a Pd-catalyzed asymmetric allylic alkylation (AAA)[3–6] of a ketone enolate. The methodological development described previously[7,8] sets a starting point for our retrosynthetic blueprint depicted in Scheme 1. The route envisioned was to form the central six-membered ring at a late stage of the synthesis via an intramolecular Friedel–Crafts acylation of acid **3** (see Supporting Information). The chiral cyclopentanone would stem from the ketone enolate derived from **5**.



Scheme 1. Synthetic strategy envision for hamigeran B.

Racemic **5** was readily prepared from commercially available 2-methylcyclopentanone via a one-pot tandem formylation/vinylogous etherification sequence. The palladium-catalyzed AAA of **5** with allyl acetate afforded the allylated product **4** in 77% yield and 93% *ee*, by using 0.5 mol% of π-allylpalladium chloride dimer and 1 mol% (*R*,*R*) "standard" Trost ligand (see Scheme 1).[3b]

Reaction of **4** with two equivalents of lithium dimethylcuprate afforded the ketone **7** in 89% yield as a 1:1 mixture of diastereomers. The vinyl triflate **8** was then obtained in 87% yield by treatment of ketone **7** with LDA and *N*-phenyltrifluoromethanesulfonimide. We were able to form the C4a–C5 bond via a Suzuki cross-coupling reaction between aryl boronic **9** (synthesized in three steps from commercially available 2-methoxy-6-methylaniline[9]) and vinyl triflate **8** in 94% yield in spite of the extreme steric congestion. Carboxylic acid **3** was obtained in two steps. First, selective oxidation of the terminal olefin in the presence of the sterically congested tetrasubstituted olefin by the dihydroxylation/periodate cleavage sequence afforded aldehyde **13** in 86% yield. Jones oxidation transformed the intermediate aldehyde to the carboxylic acid **3** in 95% yield (Scheme 2).



Scheme 2. Synthesis of carboxylic acid **3**. a) NaOMe, HCO_2Et, PhH, 0°C to rt, then *p*TsOH, *t*BuOH, reflux, 61%. b) i) LDA, DME, −78°C to 0°C. ii) *t*BuOH, Me_3SnCl, DME, 0°C. iii) 0.5 mol% $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 1 mol% (*R*,*R*)-ligand, allyl acetate, DME, −78°C to rt, 77%. c) $LiCuMe_2$, Et_2O, −20°C to rt, 89%. d) LDA, $PhNTf_2$, THF, 87%. e) 2 equiv arylboronic acid **9**, 2.5 mol% $[Pd(PPh_3)_4]$, KBr, K_3PO_4, dioxane, 85°C, 94%. f) 1.3 mol% OsO_4, NMO, THF/H_2O, 0°C to rt, then $NaIO_4$, THF/H_2O, 86%. g) Jones reagent, acetone, 75%.

Under the acidic conditions of the Jones oxidation we also observed the formation of a by-product in 5% yield. The NMR analysis of this side product allowed us to assign its structure as a product of a Friedel–Crafts acylation reaction. Unfortunately, NOE experiments on the compound provided evidence that the regioselectivity of the acylation was not *ortho* as we anticipated, but actually *para* to the methoxy directing group. Indeed, the aromatic methoxy group showed NOE correlations to two aromatic protons at δ 6.66 and 6.80, the aromatic methyl group showed a NOE correlation to the aromatic proton at δ 6.66 and a methyl group of by the isopropyl moiety showed correlation to the aromatic proton at δ 6.80 (Figure 2).

This result led us to assume that the preferred regioselectivity of the Friedel–Crafts acylation is in the *para* position to the alkoxy directing group. In order to confirm this assumption, we decided to perform the Friedel–Crafts acylation on the acyl chloride in the presence of a Lewis acid promoter, assuming that the Lewis acid would simultaneously coordinate the aromatic alkoxy substituent and the acid chloride in order to bring the *ortho* position in close proximity to the electrophilic center. We treated the in situ formed acyl chloride of **3** with 3.5 equivalents of aluminium chloride in benzene. However, isolation and characterization of the crystalline compound formed indicated that under those reaction conditions, we had obtained the tetracyclic product **12**. This product presumably arose from an initial intramolecular Friedel–Crafts acylation and, in the presence of HCl generated in the course of the reaction, a subsequent Frie-

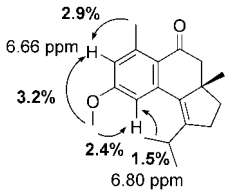
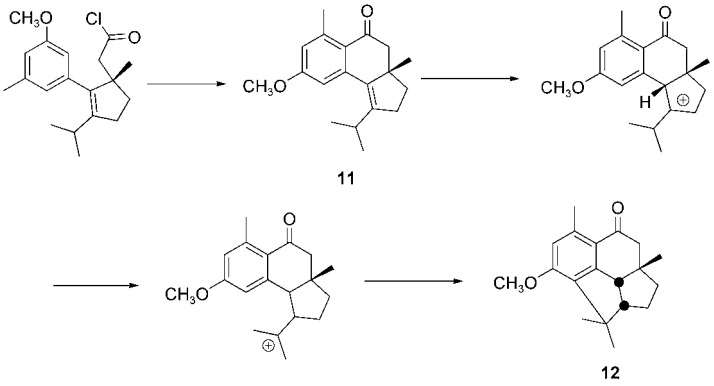


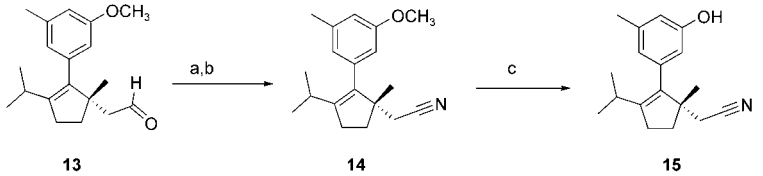
Figure 2. NOE correlations for **11**.

del–Crafts alkylation took place. Under protic conditions, formation of the tertiary non-benzylic cation is preferred due to carbonyl group destabilizing the benzylic cation. 1,2-Hydride shift (or elimination to exocyclic olefin followed by protonation) produced the tertiary isopropyl cation which then underwent electrophilic aromatic substitution (Scheme 3).

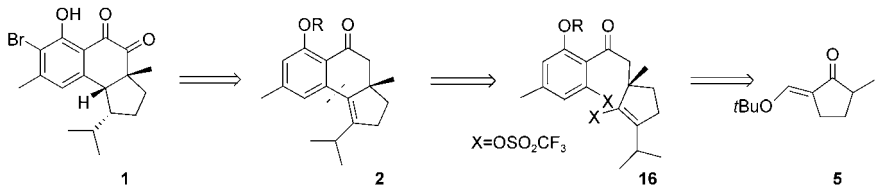


Scheme 3. Proposed mechanism for the formation of **12**.

Following these results, we decided to perform the intramolecular Friedel–Crafts acylation on the free phenol, assuming that it should be a better *ortho*-directing group, with a nitrile moiety as the electrophilic partner. Indeed, there is one precedent in the literature of an exclusive *ortho* α-chloroacetylation of phenols using a combination of boron trichloride (BCl_3) and aluminium trichloride ($AlCl_3$).[10] We treated aldehyde **13** with hydroxylamine to give the corresponding oxime[11] as a mixture of isomers, which was dehydrated under neutral and mild conditions using a catalyst system of [$RuCl_2$(*p*-cymene)]$_2$/molecular sieves[12] to give nitrile **14** in 75% yield from aldehyde **13**. The phenol was then unmasked by treatment with boron tribromide to give **15** in 85% yield (Scheme 4).



Scheme 4. Formation of nitrile **15**. a) $NH_2OH{\cdot}HCl$, CH_3CO_2Na, CH_3CN/H_2O, 1 h, rt, 98%. b) [$RuCl_2$(*p*-cymene)]$_2$, MS 4 Å, CH_3CN, 80 °C, 15 min, 76%. c) BBr_3, CH_2Cl_2, −78 °C to 0 °C, 85%.



Scheme 5. Second retrosynthetic analysis.

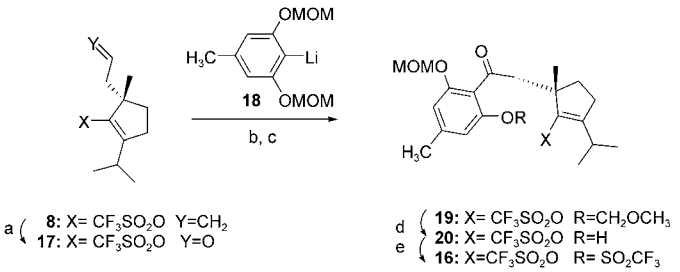
Unfortunately, no reaction was observed when phenol **15** was treated with BCl_3 and $AlCl_3$ in CH_2Cl_2. As rare earth metal trifluoromethanesulfonates were found to be efficient catalysts for Friedel–Crafts acylation and alkylation,[13] we also treated phenol **15** with a catalytic amount of [$Yb(OTf)_3$], prepared from the corresponding oxide Yb_2O_3 and trifluoromethanesulfonic acid.[14] However, no reaction was observed and the starting material could be recovered.

Unfortunately, this route was thwarted by the preferred regioselectivity *para* to the alkoxy directing group. Thus, we decided to revise our strategy for closing the central six-membered ring considering the construction of C11a–C11 bond first and then establish the C4a–C5 bond via an intramolecular palladium-catalyzed, distannane-mediated reductive coupling of an aryl triflate with a vinyl triflate (Scheme 5).

Our new strategy began with intermediate **8** and proceeded along the lines depicted in Scheme 6. The aldehyde **17** derived from the vinyl triflate **8** by an oxidation of the terminal olefin in the presence of the more electron-deficient and sterically congested tetrasubstituted olefin. Dihydroxylation/periodate cleavage sequence afforded **17** in 94% yield. Direct reaction with lithiated dimethoxymethylorcinol **18** followed by oxidation with Jones reagent gave the full carbon skeleton of the target. Under the acidic conditions of the Jones oxidation, a small percentage of the ketone was also monodeprotected to afford the phenol **20** (8%). No bis-deprotected product was ever observed. Deprotection of one of the two equivalent methoxymethyl protecting groups to afford **20** was accomplished in 56% yield from **19** by stirring in the presence of 9 M H_2SO_4. To complete the synthesis of the cyclization precursor, phenol **20** was treated with triflic anhydride in the presence of pyridine to afford **16** in excellent yield (95%). The stage is now set for the final carbon–carbon bond forming reaction to close the central six-

membered ring and complete the carbon skeleton of hamigeran B.

The transformation we propose is an intramolecular palladium-catalyzed, distannane-mediated reductive coupling of an aryl triflate with a vinyl triflate (Figure 3).



Scheme 6. Synthesis of substrate **16**. a) cat. OsO_4, NMO, THF/H_2O then $NaIO_4$. b) Et_2O, −78 to 5, 94%. c) Jones reagent, acetone, 78%. d) aq. H_2SO_4, THF, 56%. e) $(CF_3SO_2)_2O$, pyridine/CH_2Cl_2, 95%.

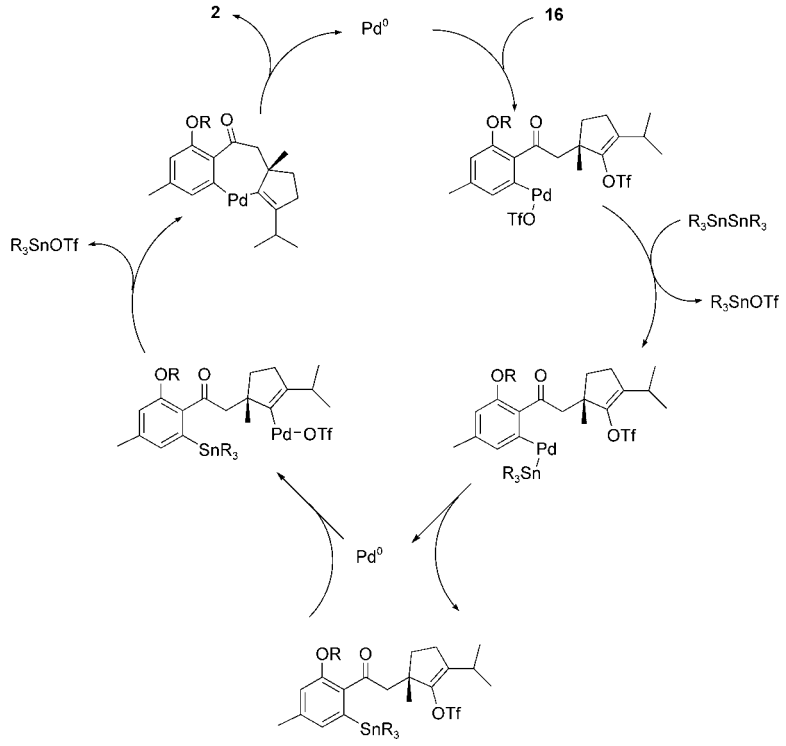


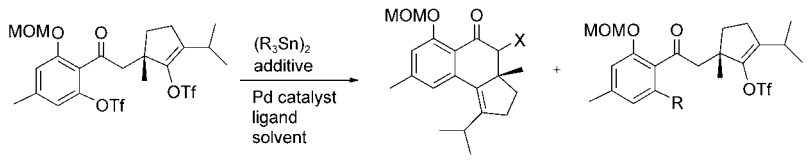
Figure 3. Aryl triflate/vinyl triflate coupling.

An intermolecular Stille reaction between the aryl triflate and the distannane afforded an arylstannnane intermediate that could immediately cyclize under the reaction conditions with the vinyl triflate via an intramolecular Stille reaction. It is also reasonable to propose a vinylstannane intermediate that cyclizes with the aryl triflate, but the vinyl triflate is far more sterically congested, as well as less electronically activated for oxidative addition than the aryl triflate. Such intramolecular reductive Stille couplings are known for aryl halide/aryl halide,[15] aryl triflate/aryl triflate,[15] aryl halide/vinyl triflate,[16] and vinyl triflate/vinyl halide[17] as well as allyl ester/allyl ester[18] coupling partners, so the aryl triflate/vinyl triflate reductive coupling is a reasonable proposition, even though no specific intramolecular or intermolecular precedent exists. Our proposed coupling reaction will be especially challenging due to the extreme steric congestion surrounding the vinyl triflate.

Several parameters were examined, including solvent, distannane, additive, palladium source, and exogenous ligands. Table 1 shows that no conditions were found that yielded any trace of **2**. As a starting point for investigation, the reaction conditions reported for the synthesis of arylstannanes from aryl halides and distannanes were chosen.[19] However, catalytically inactive palladium black crashed out of the reaction mixture quickly upon heating, and only **16** and phenol **20** were recovered from the reaction mixture, the latter presumably formed by hydrolysis of the aryl triflate by adventitious water (entry 1). To stabilize the palladium species in solution, we switched to more donating solvents such as THF and DMF and added exogenous triphenylarsine ligand. Triphenylarsine was chosen as the initial ligand because of its known ability to aid intermolecular Stille couplings of arylstannanes with vinyl triflates.[20] Indeed, doing both, precluded precipitation of palladium black and consequently led to higher conversions of the starting material. While none of the desired cyclized product was observed, using THF as the solvent led to the promising isolation of the intermediate arylstannane **22** in 41% yield, as well as the reduced product **23** in 11% yield (entry 2). This suggests that the subsequent coupling reaction with the vinyl triflate is very slow, as we had expected from the high degree of steric congestion.

Therefore, we tried two ideas to facilitate the reaction despite the steric congestion around the vinyl triflate. First, we added stoichiometric amounts of lithium chloride to the reaction mixture because of its known ability to accelerate the reactivity of triflates in cross-coupling reactions by facilitating transmetalation. Next, we switched from bis(tributyltin) to the less sterically demanding hexamethylditin. However, switching to hexamethylditin actually gave worse results (entry 2 vs 3, entry 5 vs 6). Employing a huge excess of lithium chloride and hexamethylditin in THF also gave inferior results (entry 4), although it

Table 1. Attempts to cyclize: selected conditions.[a]



16

2: X=H
21: X=CF_3SO_2O

20: R=OH
22: R=$SnBu_3$
23: R=H

Entry	Solvent	R	LiCl	$AsPh_3$	Yield
1	$PhCH_3$[b]	Bu	none	none	13% **20** and recovered **16**
2	THF[b]	Bu	none	10 mol%	41% **22**, 11% **23**, 37% **16**
3	THF[b]	Me	none	10 mol%	no reaction
4[d]	THF[b]	Me	6.0 equiv	none	mostly **16**
5	DMF[c]	Bu	3.0 equiv	40 mol%	no **16**, 29% **21**
6	DMF[c]	Me	3.6 equiv	40 mol%	complex mixture, including **16**, but no **21**

[a] All reaction were performed with $[Pd(PPh_3)_4]$ as the Pd source. [b] Heated to reflux for about 12 h. [c] Heated to 70 °C for about 12 h. [d] Corey's conditions for cyclization of a vinyl triflate with a vinyl bromide. See ref [17].

worked successfully for the Corey group to cyclize a vinyl bromide with a vinyl triflate. We chose to revert back to bis(tributyltin) and to continue employing three equivalents of lithium chloride as an additive in addition to triphenylarsine as the exogenous ligand. Choosing DMF as the new solvent gave the most promising result (entry 5). Complete consumption of the starting material was witnessed, and a product **21** was isolated in 29% yield that had ^{1}H NMR spectral attributes that were suggestive of a tricyclic structure. Coupled with low-resolution mass spectroscopy data (GC-MS), we have tentatively assigned the structure of **21** to be that depicted above.

A potential mechanism to arrive at **21** from **16** is depicted in Figure 4. Following oxidative addition of palladium(0), carbopalladation of the tetrasubstituted olefin forms the tricycle. Expulsion of the triflate leaving group yielded the desired tricycle **2** and palladium triflate. Triflate transfer from the palladium(II) species to the tricycle concomitantly reduced the palladium(II) species to a palladium(0) species to regenerate the catalytic cycle. Further investigations to optimize the formation of **21** and delineate the reaction mechanism were severely thwarted by the capriciousness and irreproducibility of the reaction.

Other parameters such as palladium source and ligand were also investigated but didn't give any successful results. Therefore, we decided to reconsider the construction of the C4a–C5 bond via an intramolecular palladium catalyzed Heck reaction of an aryl triflate with an olefin. This idea was supported by the isolation of the by-product **21** in the previous study.

Heck strategy: The formation of **21** suggested that a Heck-type strategy might be viable. Oxidative addition of palladium(0) to the sterically more accessible aryl triflate set the stage for the carbopalladation of a trisubstituted olefin to form tricycle **24**, after β-hydrogen elimination. The Heck strategy involving attack on the π-system of the double bond reduces the steric congestion relative to the oxidative addition to the vinyl triflate. Further removal of the vinyl triflate reduces the steric congestion for the carbopalladation. Furthermore, the formation of a six-membered ring via a 6-*exo-trig* mode is less sterically demanding and therefore favored. Finally, the Heck reaction should lead to a trisubstituted olefin after *syn* elimination of the palladium species which should be easier to hydrogenate in the following step (Scheme 7).

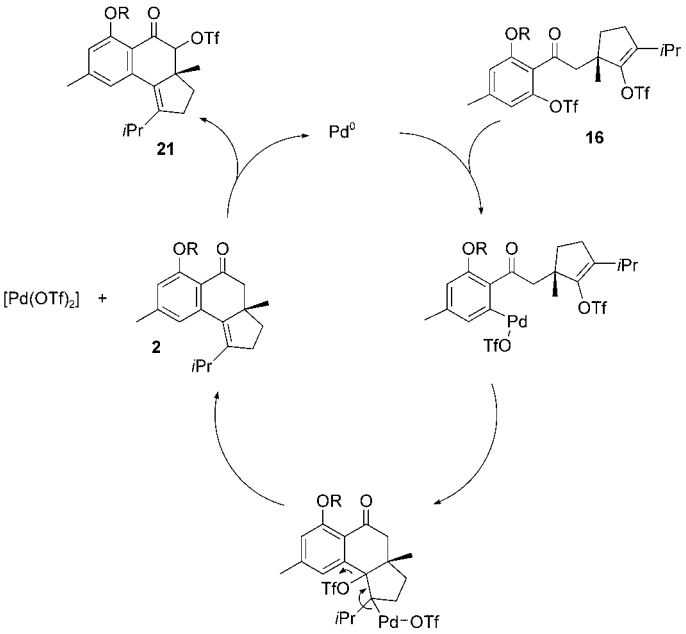
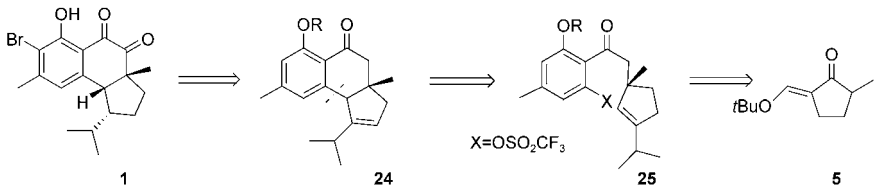


Figure 4. Proposed mechanism for the formation of **21**.

Our new strategy began with intermediate **17** which reacted with lithiated dimethylorcinol **26**. The change in the pro-



1 24 25 5

Scheme 7. Final retrosynthetic analysis.

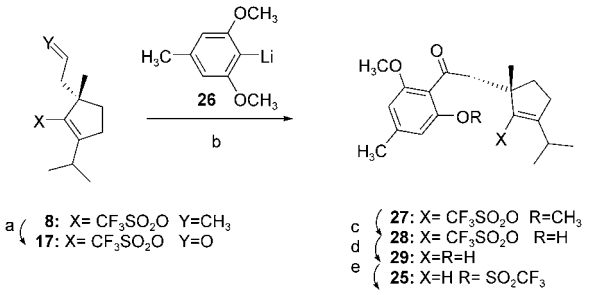
tecting group was only directed towards a higher yielding synthesis. Therefore, DME was employed as solvent at low temperature (−55 °C) to guarantee the reproducibility of the reaction. The resultant benzylic alcohol was then immediately oxidized with Dess–Martin periodinane in buffered medium to avoid elimination of the activated benzylic alcohol. With the vision that the last C–C bond would be formed by an intramolecular Heck reaction,[21] the vinyl triflate was reductively cleaved to alkene **29** and the aryl ether converted to the requisite aryl triflate **25**. (Scheme 8)

We examined the intramolecular Heck reaction of the substituted cyclopentene **25**. Surprisingly, it produced two isomeric alkenes **30** and **31** in addition to the expected alkene

Table 2. Intramolecular Heck reaction of aryl triflate **25**.[a]

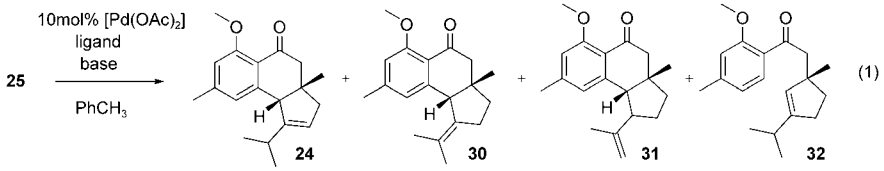
Entry	Ligand	Base	T [°C]	Conversion [%][b]	**32** [%]	**24** [%]	**30** [%]	**31** [%]
1	dppp	K_2CO_3	107	100	5	48	29	4
2	dppp	PMP	107	88	29	31	14	5
3	dppp	$CsCO_3$	107	100	2	37	18	21
4	dppe	K_2CO_3	107	76	6	42	19	10
5	dppb	K_2CO_3	107	100	5	58	14	15
6	Bdbpp	K_2CO_3	107	86	8	8	38	26
7	Bdbpb	K_2CO_3	107	83	8	25	39	6

[a] All reactions performed with 10 mol % $[Pd(OAc)_2]$, 20 mol % ligand, 3 equiv base, with a concentration of $c = 0.1$ M in toluene and cycles of freeze, pump, thaw. [b] Determinated by GC of the crude. [c] Bdbpp = 1,3-bis(dibenzophospholyl)propane, Bdbpb = 1,3-Bis(dibenzophospholyl)butane.



Scheme 8. Synthesis of substrate **25** for Heck reaction. a) cat. OsO_4, NMO, THF/H_2O, then add $NaIO_4$. b) i) DME, −55 °C. ii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 75 % from **8**. c) BCl_3, CH_2Cl_2, −20 °C, 86 %. d) 10 mol % $Pd(OAc)_2$, 20 mol % dppf, HCO_2H, $(C_2H_5)_3N$, DMF, 70 °C, 1 h, 94 %. e) $(CF_3SO_2)_2O$, pyridine/CH_2Cl_2, 0 °C, 94 %.

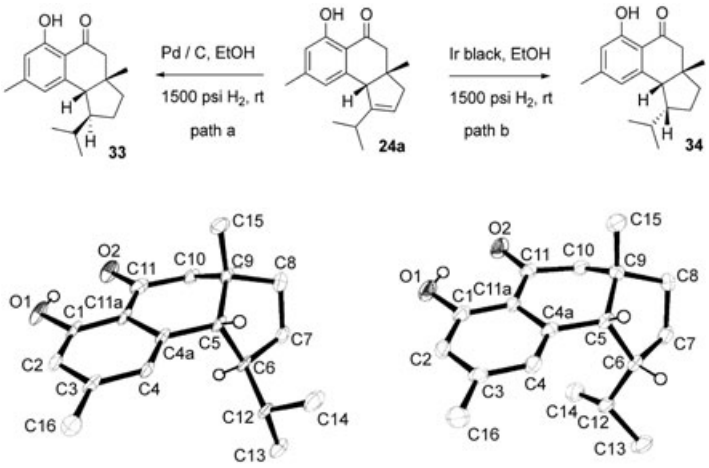
24 [Eq. (1)], surprisingly since it involves a clearly highly strained tetrasubstituted double bond exocyclic to the ring. The assessment of the relative stereochemistry of the products *syn* to the C-9 methyl group was proved by NOE experiment. Therefore, the stereodiscrimination during the C–C bond formation was fully controlled by the C-9 quaternary center, installed by the asymmetric allylic alkylation. Reaction conditions were surveyed to maximize the formation of **24** and guarantee the reproducibility of the reaction which turned out to be somewhat capricious. The latter was rapidly addressed by performing successive freeze-pump-thaw cycles on the solvent to remove any trace of oxygen. Furthermore, the use of carbonate rather than tertiary amine bases minimizes the problem of simple hydrogenolysis of the triflate (entry 1 vs 2, Table 2). With either dppe or dppp as ligands,[22] the desired alkene **24** was isolated in 42–48 % yield which increased to 58 % with dppb.[23]



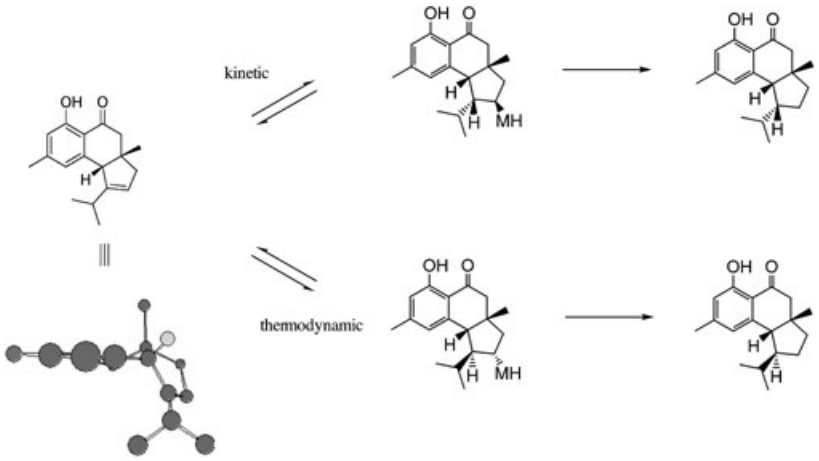
Hydrogenation from the least hindered convex face to give the desired stereochemistry of C-6 seemed to be straightforward. To avoid reduction of the carbonyl group, the free phenol was liberated with BBr_3 (CH_2Cl_2, −78 °C). Upon hydrogenation over Pd/C, a single diastereomer did result. X-ray crystallography, however, revealed the product **33** to have exclusively the C-6 *epi* configuration (Scheme 9, path a).

Hypothesizing that this product must arise by an equilibration in the semihydrogenation intermediate because the final reductive elimination step is too slow as summarized in Scheme 10, attention turned to iridium since it is known to minimize such equilibrations.[24,25] Gratifyingly, hydrogenation once again proceeded with complete diastereoselectivity (Scheme 9, path b). X-ray crystallography confirmed the correct stereochemistry as in structure **34** for all centers.

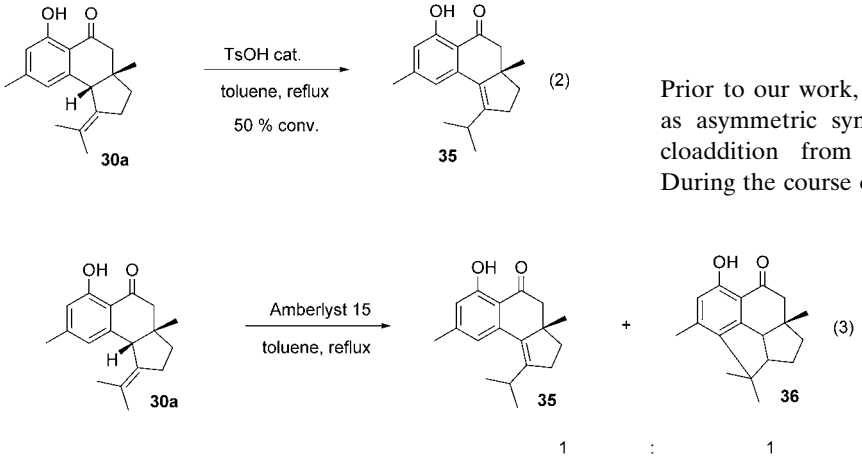
It is noteworthy to mention that no hydrogenation conditions were found to make the tetrasubstituted double bond **30a** react. Nevertheless, this product could be separated from **24a** by flash chromatography. However, we focused our attention on the isomerization of the quaternary double bond under acidic conditions. By using *p*-toluenesulfonic acid as catalyst in refluxing toluene led to the thermodynamically more stable conjugated double bond **35** which proved to be unreactive as well under all hydrogenation conditions [Eq. (2)]. By using Amberlyst 15 as a catalyst provided a 1:1 mixture of products arising from the non regioselective protonation of the double bond [Eq. (3)]. When the isopropylic carbocation is formed, an intramolecular Friedel–Crafts alkylation occurred to irreversibly give the tetracyclic product **36**, as previously encountered (Scheme 3).



Scheme 9. Orthogonality between the thermodynamic and kinetic control in hydrogenation by choice of catalyst.



Scheme 10. Kinetic versus thermodynamic control of diastereoselectivity of hydrogenation.



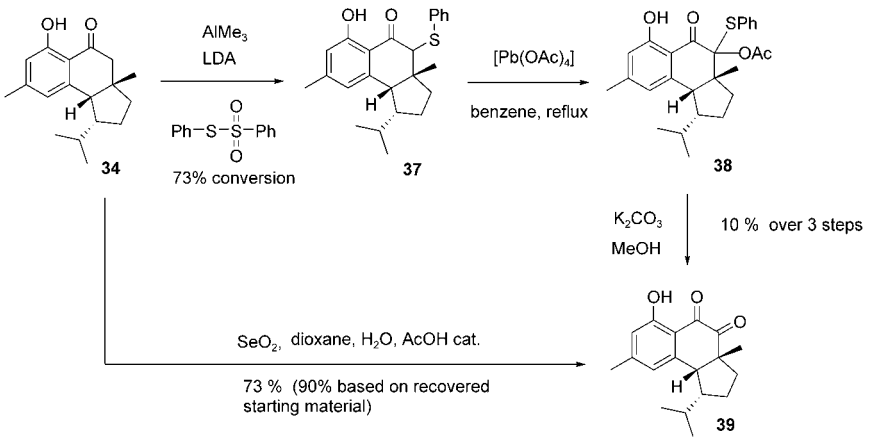
Following these results, we did not further envision the isomerization of the quaternary double bond as an attractive and efficient option to recycle our product **30a** formed during the Heck reaction and decided to attempt to minimize its formation.

At this stage, only functional group manipulation is required to arrive at the targeted structure. We first needed to oxidize the tetralone to the corresponding 1,2-diketone (Scheme 11). For this purpose, we applied a methodology developed in our group some years ago.[26] Treatment of the enolate of compound **34** with phenyl benzenethiosulfonate afforded the corresponding β-ketosulfides **37** which could be acetoxylated by using lead tetraacetate in warm benzene. The β-keto acetoxy sulfide **38** represents a monoprotected form of the 1,2-dicarbonyl compound **39** which could be unmasked by saponification of the acetate group under basic conditions. However, the yield of the overall transformation proved to be disappointingly low. The free phenol seemed to be problematic for the acetoxylation step and the conditions (K_2CO_3 in MeOH) for the saponification required examination as well.

On the other hand, selenium dioxide oxidation of **34** efficiently yielded **39**. The reaction proved to be very clean. Finally, selective monobromination *ortho* to the phenolic group completed the sequence to the natural product. This was smoothly effected by following the conditions described by Krohn,[27] which entail the slow addition via a syringe pump of stoichiometric amounts of NBS in the presence of catalytic iPr$_2$NH in CH_2Cl_2 at 0 °C. Comparison of the data to that previously reported[1,28,29] confirmed their identify.

Conclusion

Prior to our work, Nicolaou et al. reported the first as well as asymmetric synthesis utilizing a novel [4+2] photocycloaddition from *N-tert*-butyl-2-methoxy-*p*-toluamide.[28,29] During the course of our studies, Clive reported a racemic[30] and asymmetric synthesis, the latter from γ-butyrolactone and 2-bromo-6-methoxy-*p*-tolualdehyde.[31] Herein, a short and concise synthesis of hamigeran B has been achieved in 15 linear steps in 10% overall yield from 2-methylcyclopentanone. This synthesis represents the shortest reported to date[23,28–31] and highlights the efficiency of the palladium catalyzed asymmetric alkylation of ketone enolates. Indeed, that key step allowed us to introduce the quaternary center



Scheme 11. Formation of diketone **39**.

in 93% *ee*, which controls the relative configuration of the C-5 and C-6 contiguous stereocenters. Thus, one asymmetric step is necessary to install stereoselectively three stereocenters. Furthermore, the unusual nature of the structure is highlighted by two abnormal reactivities: first, the formation of an exocyclic tetrasubstituted double bond during the Heck studies and second, the high propensity to give net reduction of the trisubstituted double bond of **24a** from the more hindered face. The orthogonality between the thermodynamic and kinetic control in hydrogenation by choice of catalyst is noteworthy.

Experimental Section

Pd AAA reaction

(*S*)-2-Allyl-5-*tert*-butoxymethylene-2-methyl-cyclopentanone (4): A 1 L round bottom flask was charged with 1,2-dimethoxyethane (DME; 165 mL) and diisopropylamine (10.12 g, 14.18 mL, 100 mmol). The solution was cooled to −78 °C and *n*-butyllithium (1.6 M in hexanes, 62.4 mL, 100 mmol) was added dropwise. The resultant clear solution was stirred at −78 °C for 15 min and a solution of cyclopentanone **5** (9.115 g, 50 mmol) in DME (35 mL) was added via cannula. The resultant orange solution was stirred at 0 °C for 15 min, charged with anhydrous *tert*-butanol (25.94 g, 32.83 mL, 350 mmol), followed by a solution of trimethyltin chloride (9.96 g, 50 mmol) in DME (35 mL). The resultant red orange solution was stirred at 0 °C for 15 min and then re-cooled to −78 °C. To this solution was added a heterogeneous mixture of allyl palladium chloride dimer (219 mg, 0.6 mmol), (*R*,*R*)-Trost standard ligand (863 mg, 1.25 mmol), and allyl acetate (11.01 g, 11.89 mL, 110 mmol) in DME (35 mL). The resultant red-orange heterogeneous mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (200 mL) and the layers were separated. The aqueous layer was re-extracted twice with Et_2O (2×140 mL), and the combined organic phases were washed with water and saturated brine (1×200 mL each) and dried over magnesium sulfate. Concentration in vacuo, drying of the crude oil under high vacuum (0.3 Torr) for 90 min and purification of the residue on silica gel (15% ether/petroleum ether) afforded **4** as yellow oil (8.56 g, 77%). R_f=0.40 (20% ethyl acetate/petroleum ether); determination of enantiomeric excess: chiral GC (cyclosil B, isotherm 120 °C), t_R(major)=70.162 min, t_R(minor)=71.370 min; $[\alpha]_D^{26.9}$=−75.2° (*c* = 1.47, chloroform, 93% *ee*); IR (neat): $\tilde{\nu}$ = 2977, 2868, 1708, 1631, 1456, 1371, 1264, 1206, 1156, 980, 945 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.51 (t, *J*=2.3 Hz, 1H), 5.76–5.68 (m, 1H), 5.05–5.00 (m, 2H), 2.49–2.38 (m, 2H), 2.19–2.11 (m, 2H), 1.84 (ddd, *J*=12.8, 7.1, 8.2 Hz, 1H), 1.58 (ddd, *J*=12.8, 6.4, 7.7 Hz, 1H), 1.35 (s, 9H), 1.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 210.8, 149.0, 134.6, 117.6, 115.2, 79.7, 49.4, 41.2, 32.5, 28.2, 22.0, 21.2; elemental analysis calcd (%) for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found C 75.84, H 10.18.

Heck reaction

(3*aS*,9*bR*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,9b-tetrahydro-cyclopenta[*a*]naphthalen-5-one (24): The solvent used for the reaction was carefully degassed by successive freeze thaw cycles. To a solution of $[Pd(OAc)_2]$ (107 mg, 0.48 mmol, 10 mol%) in toluene (24 mL) in a 100 mL round bottom flask, was added 1,3-(diphenylphosphino)butane (dppb) (409 mg, 0.96 mmol, 20 mol%). After 15 min, a solution of triflate **25** (2.084 mg, 4.8 mmol) in toluene (24 mL) was added, followed by K_2CO_3 (1.904 g, 14.4 mmol, 3 equiv). After 5 min, the reaction flask was fitted with a reflux condenser and heated at 107 °C for 8 h (oil bath already at desired temperature). The product distribution is then determinated by GC.

After cooling down the reaction mixture, the mixture is filtered on silica gel (5% to 60% ether/petroleum ether) to afford the Heck products (1.2 g, 91%) containing 58% of the desired endocyclic double bond **24**: R_f=0.25 (50% ether/petroleum ether); $[\alpha]_D^{26.5}$ =170.1(±0.5)° (*c* = 0.39, chloroform, 93% *ee*); IR (neat): $\tilde{\nu}$ = 2957, 2869, 1681, 1606, 1567, 1455, 1413, 1328, 1298, 1103, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.69 (s, 1H), 6.65 (s, 1H), 5.40–5.39 (m, 1H), 3.87 (s, 3H), 3.56 (s, 1H), 2.80 (d, *J*=14.5 Hz, 1H), 2.37 (s, 3H), 2.31 (d, *J*=14.5 Hz, 1H), 2.23–2.12 (m, 3H), 1.22 (s, 3H), 1.11 (d, *J*=6.7 Hz, 3H), 0.77 (d, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.4, 159.4, 151.5, 145.2, 144.5, 122.9, 121.0, 119.5, 110.6, 57.0, 55.8, 50.6, 45.1, 44.4, 27.2, 25.7, 22.3, 22.2, 21.4; HR-MS: *m*/*z*: calcd for $C_{19}H_{24}O_2$: 284.1776, found 284.1784 $[M]^+$.

Hydrogenation

(1*R*,3*aS*,9*bS*)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[*a*]naphthalen-5-one (34): Ir black from Aldrich (60 mg, 0.31 mmol, 15 mol%) was added to a solution of phenol **24a** (562 mg, 2.078 mmol) in EtOH (21 mL). The heterogeneous solution was then charged with 1500 psi of hydrogen pressure. The mixture was stirred at room temperature for 16 h and filtered over Celite to leave the desired stereoisomer **34** as a white solid (564 mg, 99%). R_f=0.60 (50% ether/petroleum ether); m.p. 142–143 °C (EtOAc/hexane); $[\alpha]_D^{25}$ = −59.9° (*c* = 0.78, chloroform, 93% *ee*); IR (neat): $\tilde{\nu}$ = 2952, 2872, 2360, 1635, 1566, 1467, 1450, 1364, 1350, 1307, 1256, 1225, 1190, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 12.48 (s, 1H), 6.60 (s, 1H), 6.52 (s, 1H), 3.00 (d, *J*=11.7 Hz, 1H), 2.67 (d, *J*=17.3 Hz, 1H), 3.53–2.46 (m, 1H), 2.32 (s, 3H), 2.25 (dd, *J*=17.3, 1.4 Hz, 1H), 1.86–1.81 (m, 1H), 1.70–1.55 (m, 4H), 1.10 (s, 3H), 0.72 (d, *J*=6.7 Hz, 3H), 0.48 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 205.2, 162.3, 147.5, 144.7, 123.2, 115.5, 114.6, 51.8, 49.2, 46.0, 43.8, 39.6, 28.6, 26.9, 25.6, 23.5, 22.2, 18.2; elemental analysis calcd (%) for $C_{18}H_{24}O_2$: C 79.37, H 8.88; found: C 79.50, H 8.83.

(1*R*,3*aR*,9*bR*)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione (39): SeO_2 (132 mg, 1.18 mmol) was added to a solution of phenol **34** (322mg, 1.18 mmol) in dioxane (7 mL), H_2O (225 μL) and 1 drop AcOH. The resultant suspension was stirred for 24 h at 100 °C. The yellow solution was then cooled down to room temperature and filtered through a silica gel pad to remove inorganic products. After evaporation, the crude mixture was purified by chromatography on silica gel (5% to 10% Et_2O/PE) to give **39** as a yellow solid (248 mg, 73%) together with starting material **34** (60 mg, 90% based on reovered starting material). **39**: R_f=0.23 (10% ether/petroleum ether); m.p. 92–93 °C; $[\alpha]_D^{23.7}$ = −189.0° (*c* = 0.29, dichloromethane); IR (neat): $\tilde{\nu}$ = 2959, 1725, 1634, 1567, 1453, 1368, 1338, 1303,

1217, 1197, 1154, 1098, 1035, 936, 851, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 11.92 (s, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 3.39 (d, J = 9.1 Hz, 1H), 2.61 (ddd, J = 13.3, 7.7, 5.5 Hz, 1H), 2.38 (s, 3H), 2.30–2.24 (m, 1H), 1.83–1.76 (m, 1H), 1.70–1.64 (m, 1H), 1.57–1.51 (m, 1H), 1.29 (s, 3H), 1.24–1.16 (m, 1H), 0.54 (d, J = 6.6 Hz, 3H), 0.42 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 200.1, 184.3, 164.6, 150.8, 144.1, 123.4, 116.7, 116.2, 56.8, 56.4, 51.4, 33.8, 28.1, 26.9, 24.4, 23.2, 22.5, 19.8; elemental analysis calcd (%) for $C_{18}H_{22}O_3$: C 75.50, H 7.74; found: C 75.71, H 7.49.

Hamigeran B (1): A solution of NBS (50 mg, 0.03 mmol) in CH_2Cl_2 (20 mL) was added dropwise over ≈4 h (syringe pump) to a stirred and cooled (0 °C) solution of diketone **39** (80 mg, 0.028 mmol) and iPr$_2$NH (ca. 0.2 mL, 0.14 mmol) in CH_2Cl_2 (40 mL). The ice bath was removed and the mixture was stirred for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 7:3 CH_2Cl_2/toluene gave hamigeran B (86 mg, 85%) as a yellow solid. R_f = 0.36 (30% toluene/CH_2Cl_2); m.p: 162–163 °C (lit.[1] m.p. 163–165 °C;) $[\alpha]_D^{25.8} = -211.1°$ (c = 0.15, dichloromethane); IR (neat): $\tilde{\nu}$ = 2958, 2361, 1996, 1725, 1634, 1540, 1436, 1397, 1280, 1169, 1030, 778, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 12.6 (s, 1H), 6.82 (s, 1H), 3.39 (d, J = 9.2 Hz, 1H), 2.64 (ddd, J = 13.1, 7.6, 5.2 Hz, 1H), 2.51 (s, 3H), 2.34–2.27 (m, 1H), 1.84–1.77 (m, 1H), 1.72–1.65 (m, 1H), 1.58–1.52 (m, 1H), 1.29 (s, 3H), 1.22–1.16 (m, 1H), 0.51 (d, J = 6.7 Hz, 3H), 0.45 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 199.0, 184.4, 160.8, 150.2, 142.7, 124.2, 117.2, 111.5, 56.9, 56.2, 51.2, 33.7, 28.1, 26.7, 24.4, 24.3, 23.3, 19.7.

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