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An Asymmetric Synthesis of Hamigeran B via a Pd Asymmetric Allylic Alkylation for Enantiodiscrimination

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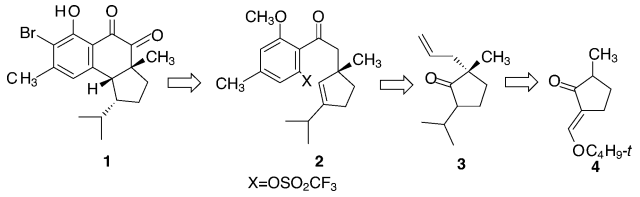
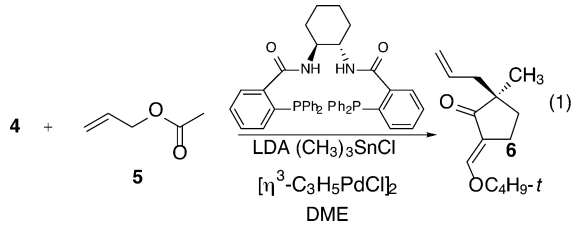
Hamigeran B (**1**), a metabolite isolated from the poecilosclerid sponge *Hamigera tarangaensis* Bergquist and Fromont, exhibits 100% virus inhibition against both herpes and polio viruses with only slight cytotoxicity throughout the host cells.[1] Its structural motif combined with the biological activity stimulates the development of a practical synthesis that can facilitate exploration of the chemical biology of such structural types represented by these scarce natural products. Nicolaou reported the first as well as asymmetric synthesis utilizing a novel [4 + 2] photocycloaddition from *N*-*tert*-butyl-2-methoxy-*p*-toluamide.[2] During the course of our studies, Clive reported a racemic[3] and an asymmetric synthesis, the latter from α-butyrolactone and 2-bromo-6-methoxy-*p*-tolualdehyde.[4] 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)[5] of a ketone enolate derived from **4** (see Scheme 1). In this communication, we report the results

Scheme 1. Retrosynthetic Analysis



of this latter study which then led to an effective convergent approach to hamigeran B. During the course of this study, we uncovered a most unusual dependence of diastereoselectivity in a heterogeneous catalytic hydrogenation.

Alkylation of the lithium enolate of **4**[6] was examined under conditions developed earlier for six-membered ring ketones (eq 1).[7]



Initially, the results were very encouraging. At room temperature, the reaction gave the alkylated product **6** in 61% yield and 64% ee. At −20 °C, the ee rose to an astonishing 92−96%. However, upon switching to a fresh bottle of *n*-butyllithium to generate LDA, repetition of the reactions led to ee's of 5−12% (Table 1, entry 1). Lowering the temperature increased the ee somewhat (entry 2) but still far from the earlier results. Speculating that the earlier bottles of *n*-butylithium had higher levels of lithium alkoxide led to the addition of *tert*-butyl alcohol, which should form a relatively non-nucleophilic alkoxide. While 1 equiv of *tert*-butyl alcohol had little

Table 1. Pd AAA of Enol Ether **4**[a]

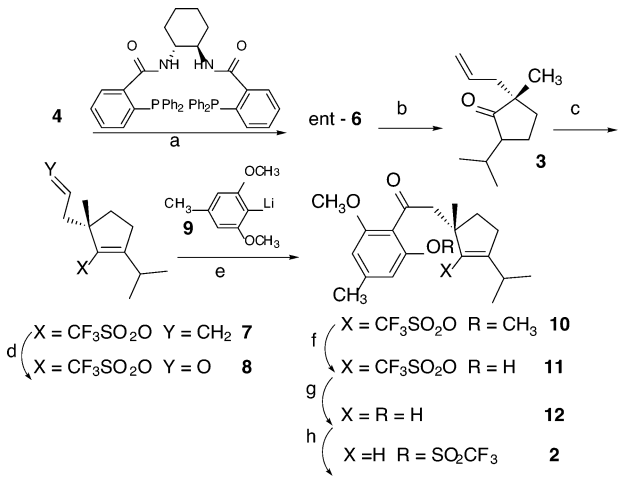
entry	*t*-butanol	temp (°C)	yield (%)	ee (%)
1	none	0	93	12
2	none	−60	80	29
3	1 equiv	rt	85	15
4	3 equiv	rt	86	79
5	7 equiv	rt	87	91
6[b]	7 equiv	rt	83	95

[a] All reactions were performed with 1.1 equiv of allyl acetate **5a**, 1 equiv of trimethyltin chloride, 2 equiv of LDA, 2.5 mol % of $[\eta^3\text{-}C_3H_5PdCl]_2$, and 5 mol % (*S*,*S*)-ligand. [b] For this run, 1 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$ and 2 mol % (*S*,*S*)-ligand were used.

effect (entry 3), addition of 3 equiv quickly put the reaction back into the range of the first results (entry 4). Increasing the amount to 7 equiv returned the ee to >90% (entry 5). Interestingly, decreasing the catalyst loading saw a further increase in the ee (entry 6). This last set of conditions is very robust and scales up nicely.

With asymmetric alkylation resolved, attention turned to implementing a synthesis of hamigeran B (Scheme 2). To obtain the

Scheme 2. Synthesis of Substrate **2** for Heck Reaction[a]



[a] (a) As in Table 1, entry 6, 77%, 93% ee. (b) $(CH_3)_2CuLi$, ether, −20 °C, 89%. (c) LDA, $PhN(SO_2CF_3)_2$, THF, 87%. (d) cat. OsO_4, NMO, THF, H_2O then add $NaIO_4$. (e) i. DME, −55 °C. ii. Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 75% from **7**. (f) BCl_3, CH_2Cl_2, −20°, 86%. (g) 10 mol % $Pd(OAc)_2$, 20 mol % dppf, HCO_2H, $(C_2H_5)_3N$, DMF, 70°, 94%. (h) $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine, 0 °C, 94%.

stereochemistry assigned to hamigeran B, the mirror image alkylation was performed simply by changing the chirality of the ligand. The versatility of the alkoxymethylene group is illustrated by its direct conversion to the isopropyl compound **7** upon treatment with lithium dimethylcuprate.[8] While, in principle, quenching with a triflating agent should allow direct formation of the vinyl triflate **8**, the isolated ketone was converted to the vinyl triflate in a separate

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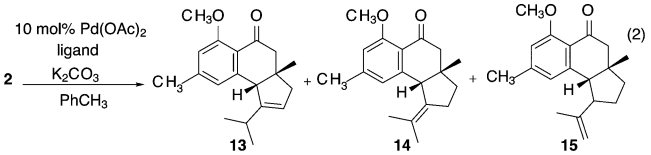
step. Oxidative cleavage of the double bond completes the synthesis of one-half of hamigeran B.

Direct reaction with lithiated dimethyl orcinol **9** followed by oxidation with the Dess−Martin periodinane gave the full carbon count of the target. With the vision that the last C−C bond would be formed by an intramolecular Heck reaction,[9] the vinyl triflate was reductively cleaved to alkene **12** and the aryl ether was converted to the requisite aryl triflate **2**. The Heck reaction produced two isomeric alkenes, **14** and **15**, in addition to the expected alkene **13**, surprisingly, since it involves a highly strained tetrasubstituted double bond exocyclic to the ring. Use of carbonate rather than tertiary amine bases minimizes the problem of simple hydrogenolysis of the triflate. With either dppe or dppp as ligands,[10] the desired alkene **13** was isolated in 42−48% yield, which increased to 58% with dppb.[11]



Hydrogenation from the least hindered face (see Figure 1) to give the desired stereochemistry of C-6 seemed to be straightforward. To avoid reduction of the carbonyl group, the free phenol

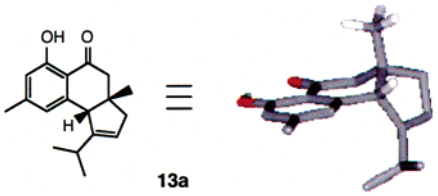
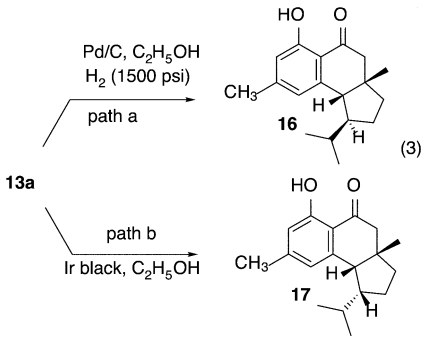
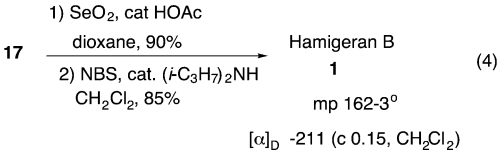


Figure 1. Conformational Depiction of Phenol **13a**.

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 **16** to have exclusively the C-6 epi configuration (eq 3, path a).



Hypothesizing that this product must arise by an equilibration in the semihydrogenation intermediate because the final reductive elimination step is too slow, attention turned to iridium since it is known to minimize such equilibrations.[12,13] Gratifyingly, hydrogenation once again proceeded with complete diastereoselectivity (eq 3, path b). X-ray crystallography confirmed the correct stereochemistry as in structure **17** for all centers. Oxidation with selenium dioxide and bromination completes the sequence (eq 4). Comparison of the data to that previously reported[1−4] confirmed their identity.



In summary, a new class of nucleophiles allows asymmetric allylation of five-membered rings in high yield and enantioselectivity. The importance of the nature of the nucleophile on the enantioselectivity is highlighted by the critical dependence on the presence of lithium alkoxides, which presumably affects the nature of the enolate clusters. The virtue of this class is revealed by a 15-step asymmetric synthesis of hamigeran B from 2-methylcyclopentanone in 10% overall yield. 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 **13a** from the more hindered face. The orthogonality between the thermodynamic and kinetic control in hydrogenation by choice of catalyst is noteworthy.

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Supporting Information Available: Full experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Derived in one pot from reaction of 2-methylcyclopentanone with ethyl formate ($NaOC_4H_9$-*t*, PhH) concentrating, diluting with *tert*-butyl alcohol, acidifying with sulfuric acid to pH 2−3, and heating at reflux in the presence of $MgSO_4$, 70% yield mp 52−53 °C.
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(11) After completion of our work, Mehta reported a strategy similar to ours that resulted in a synthesis of 6-epi-hamigeran B. In his intramolecular Heck reaction, he reports a 2:1 mixture of **13** and the simple hydrogenolysis product in a total 55−60% yield but does not report the tetrasubstituted olefin. See: Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049.
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(13) Mehta and Shinde report that variation of catalyst did not resolve the unfavorable diastereoselectivity of the hydrogenation but fail to record what catalysts were tried.

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