Natural Product Synthesis

# Stereospecific Total Synthesis of the Antiviral Agent Hamigeran B—Use of Large Silyl Groups to Enforce Facial Selectivity and to Suppress Hydrogenolysis**

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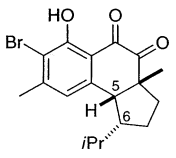
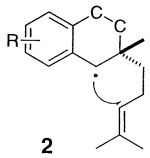
We report the stereospecific synthesis of hamigeran B (**1**, Scheme 1), which is an important member of a group of related compounds isolated[1] from a marine sponge. Hamigeran B has been found to have strong in vitro activity against




**1**




**2**

***Scheme 1.*** Hamigeran B (**1**) and the radical cyclization of **2**.

polio and herpes viruses but little cytotoxicity.[1] The compound presents a number of constructional problems, and the significant biological properties enhance the potential value of work on its synthesis. One route to hamigeran B and several congeners has been reported.[2] We aimed to deal only with the synthesis of hamigeran B itself and to do so in a stereospecific manner.

The most obvious synthetic difficulty resides in the stereochemistry at C6 (see **1**), as the bulky isopropyl group extends into the more hindered concave face of the structure. This orientation probably disqualifies methods that rely on stereochemical equilibration at C6. Likewise, radical cyclization (see **2**), which is a powerful method for making [4.3.0] bicyclic structures with *cis* ring fusion, does not[3] generate the correct stereochemistry at C6 because the required transition state is destabilized by steric interactions engendered by the isopropylidene group. Further synthetic analysis, as well as experimental work, suggested that double-bond reduction (Scheme 2, **3**→**4**), possibly directed by a suitably placed substituent, would merit detailed investigation. We recognized, however, that the double bond in **3**, being tetrasubstituted, might be resistant to hydrogenation.[4] Also, examination of Dreiding models exposed another potential difficulty: it was not obvious from the shape of **3** whether

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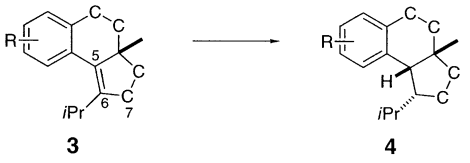
[**] We thank NSERC for financial support, Dr. R. McDonald (X-Ray Crystallography Laboratory) for crystal-structure determinations, and Professor S. Bergens and S. Fletcher for valuable advice.

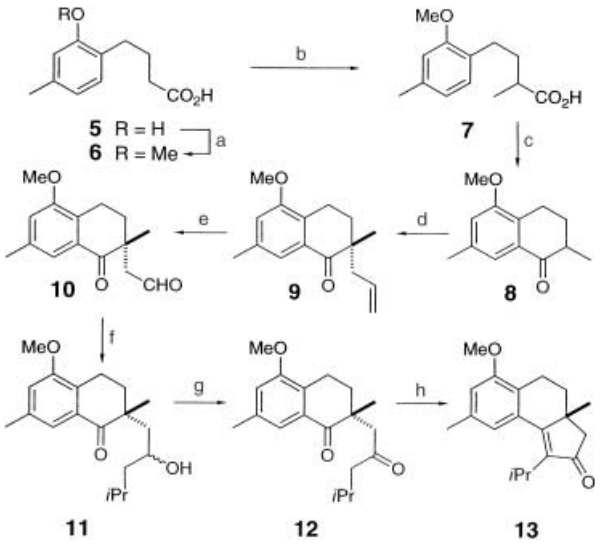
  DOI: 10.1002/ange.200351519 



***Scheme 2.*** Key transformation in the synthesis of hamigeran B (**1**).

hydrogenation would occur preferentially from the α or β face. Nonetheless, we decided to examine the approach shown in Scheme 2, and we were eventually able, through the temporary introduction of additional steric factors, to develop it into a powerful approach for solving the stereochemical problems inherent in the convex shape and substitution pattern of hamigeran B.

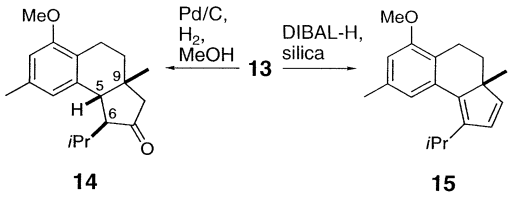
The phenolic carboxylic acid **5** (Scheme 3), easily prepared from *m*-cresol by Friedel–Crafts acylation with succinic anhydride[5] followed by Clemmensen reduction,[6] was



***Scheme 3.*** Preparation of the key intermediate **13**. Reagents and conditions: a) $Me_2SO_4$, aqueous NaOH, reflux, 12 h, 67% from *m*-cresol; b) LDA, THF, HMPA, −78°C, MeI, 96%; c) $POCl_3$, $Cl_2CHCHCl_2$, reflux, 5 h, 83%; d) LDA, THF, −78°C, allyl bromide, 91%; e) $OsO_4$, $NaIO_4$, dioxane/water 3:1, 3.5 h, 76%; f) *i*BuMgCl, $Et_2O$, −78°C, 89%; g) PCC, $CH_2Cl_2$, 3.5 h, 87%; h) aqueous EtOH, NaOH, reflux, 36 h, 98%. HMPA = hexamethylphosphoric triamide, LDA = lithium diisopropylamide, PCC = pyridinium chlorochromate.

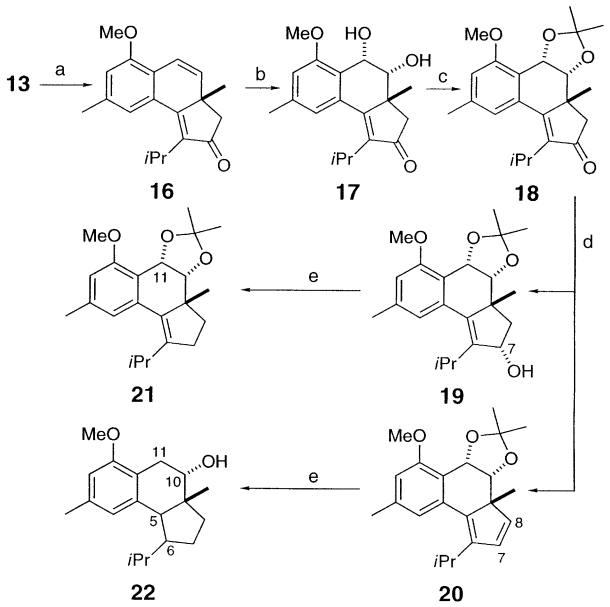
treated with $Me_2SO_4$ under alkaline conditions (**5**→**6**),[5] and then methylated[7] at the position α to the carboxy group. Cyclization, by treatment with $POCl_3$ (**7**→**8**[7]), and allylation gave the substituted tetralone **9**. Double-bond cleavage (**9**→**10**) and exposure to *i*BuMgCl at low temperature then led to keto alcohols **11**, and oxidation afforded the corresponding diketone **12**. This was cyclized under basic conditions in good yield to produce our first key intermediate, **13**.

Hydrogenation of **13** over Pd/C in MeOH ($H_2$, 345 kPa) gave the crystalline ketone **14** (Scheme 4) as the major product[8] (52% yield), which has the undesired β stereochemistry at C6, as determined by X-ray analysis. On the



***Scheme 4.*** Some transformations of enone **13**. DIBAL-H = diisobutylaluminum hydride.

assumption that the desired α stereochemistry was generated initially but that the product underwent carbonyl-mediated epimerization, we attempted to reduce ketone **13** to the corresponding allylic alcohol in order to remove that possibility. Treatment of **13** with $NaBH_4$ and $CeCl_3{\cdot}7H_20$, was unsuccessful, as the compound reacted much too slowly, but reaction with DIBAL-H (0°C to room temperature) was rapid. However, the resulting allylic alcohol is very sensitive, and exposure to silica gel during flash chromatography caused dehydration, so that the material isolated (98%) was the diene **15** (Scheme 4). Hydrogenation of this diene (Pd/C, $H_2$, 345 kPa, MeOH) did saturate the two double bonds, but an inseparable mixture (ca. 1:1 in some experiments) of stereoisomers was formed. We attributed this result to a lack of facial selectivity, and so we decided to introduce a bulky group to block the α face of ketone **13**. To this end, the ketone was dehydrogenated with DDQ (Scheme 5, **13**→**16**). Dihydroxylation (**16**→**17**) with $OsO_4$ and NMO occurred *anti* to the adjacent methyl substituent, as desired, and the stage was now set to mask the hydroxy groups with a bulky substituent, so as to direct subsequent hydrogenation exclusively to the opposite face.

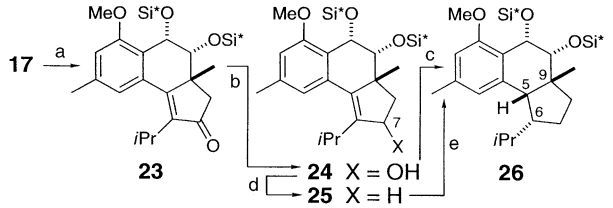


***Scheme 5.*** Reagents and conditions: a) DDQ, dioxane, reflux, 8.5 h, 78%; b) $OsO_4$, NMO, $CCl_4$/water/*t*BuOH/acetone 5:1:4:6, 13 h, 98%; c) $Me_2C(OMe)_2$, TsOH·pyridine, acetone, 4 h, 88%; d) DIBAL-H, $CH_2Cl_2$, 0°C, 8 h, 54% of **19**, 23% of **20**; e) Pd/C, $H_2$, 345 kPa, MeOH. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, NMO = 5-methylmorpholine *N*-oxide, Ts = toluene-4-sulfonyl.

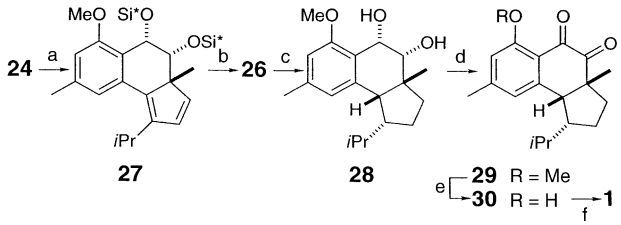
Conversion of diol **17** into ketal **18** was achieved by standard procedures, and the carbonyl group was then reduced with DIBAL-H to give a 2.3:1 mixture of allylic alcohol **19** (tentative stereochemistry shown at C7[9]) and diene **20**. Hydrogenation of **19** gave **21** and a mixture of substances lacking a benzylic oxygen at C11 (absence of $^1$H NMR signals at $\delta \approx 5$ ppm for the benzylic CH–O). With short reaction times (1 h) **21** was the major product (ca. 80% yield). Only the C7–C8 double bond of diene **20** was reduced when we used $Rh/Al_2O_3$ ($H_2$, 4826 kPa, 50 °C, MeOH), Wilkinson's catalyst ($H_2$, 2758 kPa, MeOH, 50 °C), or Raney 2800 Ni (Aldrich; 7929 kPa, 60 °C, MeOH). Hydrogenation of **20** gave **22** (92% yield, stereochemistry at C5 and C6 not established, Scheme 5). Olefin **21** did not react in refluxing THF with $BH_3$ or 9-borabicyclo[3.3.1]nonane (9-BBN). Our failure to effect hydroboration and the finding that hydrogenolysis occurred at C11 in experiments with Pd/C caused us to modify the route in a small but effective way.

With the aim of avoiding hydrogenolysis of the C11 oxygen, we decided to protect the hydroxy groups of diol **17** with substituents having sufficient bulk to hinder coordination[10,11] of the benzylic oxygen to the catalyst surface, and so we silylated the hydroxy group with $t$BuMe$_2$SiOSO$_2$CF$_3$ (Scheme 6, **17**→**23**). DIBAL-H reduction gave an allylic




***Scheme 6.*** Reagents and conditions: a) $t$BuMe$_2$SiOSO$_2$CF$_3$, $CH_2Cl_2$, 2,6-lutidine, 6 h, 84%; b) DIBAL-H, $CH_2Cl_2$, 0 °C to room temperature, 10 h, 94%; c) Pd/C, $H_2$, 345 kPa, MeOH, 18%; d) Pd/C, $H_2$, 345 kPa, MeOH, 35%; e) Pd/C, $H_2$, 345 kPa, MeOH, 93%. Si* = Si$t$BuMe$_2$.

alcohol (**23**→**24**, stereochemistry at C7 not determined). Hydrogenation of **24** provided the desired product **26** but in low yield (18%). When the reaction time was only 6.5 h, one of the products was monoene **25** (35%), and this compound could be hydrogenated in high yield to give the desired **26**. These observations showed that the hydroxy group of **24** had a deleterious effect on the outcome of our hydrogenation experiments. Accordingly, we dehydrated allylic alcohol **24** to give the corresponding diene **27** (Scheme 7). Elimination of the intermediate mesylate is slow and required higher temperatures, but the diene, once formed, was very well-behaved and could be reduced to **26** with the required relative stereochemistry at the three contiguous asymmetric centers, C5, C6, and C9. Compound **26** is crystalline, but the crystals were unsuitable for X-ray analysis. However, desilylation (Scheme 7, **26**→**28**), which required unusually harsh conditions but worked efficiently, gave a nicely crystalline diol, whose structure was determined by X-ray analysis. Diol oxidation (**28**→**29**) was easily performed under Swern conditions, and the next task was to remove the *O*-methyl group of **29**. This was done in 78% yield by treatment with LiCl in




***Scheme 7.*** Reagents and conditions: a) MsCl, $Et_3N$, $ClCH_2CH_2Cl$, room temperature for 30 min, then reflux for 8 h, 80%; b) Pd/C, $H_2$, 269 kPa, 1:1 MeOH/hexane, 36 h, 85%; c) $Bu_4NF$, THF, reflux, 24 h, 95%; d) $(COCl)_2$, DMSO, $Et_3N$, −78 °C, 1 h, room temperature, 2 h, 92%; e) LiCl, DMF, reflux, 20 h, 78%; f) NBS, $i$Pr$_2$NH, $CH_2Cl_2$, 3 h, 94%. Si* = Si$t$BuMe$_2$. DMSO = dimethyl sulfoxide, Ms = methanesulfonyl, NBS = *N*-bromosuccinimide.

refluxing DMF (**29**→**30**);[13] other standard reagents ($BBr_3$, $AlCl_3$, $Me_3SiI$) destroyed the starting methyl ether. Finally, bromination of **30** with NBS in the presence of $i$Pr$_2$NH, a reagent system known to favor *ortho* bromination of phenols,[14] gave hamigeran B (**1**) in 94% yield. The $^1$H and $^{13}$C NMR, FTIR, and MS characteristics of our synthetic material match those reported[1] for the natural product.

The special features of this synthesis are the use of very simple reactions—a fact which should make the route amenable to scale-up, the application of steric factors to ensure facial selectivity, and the protection against hydrogenolysis[15] that is afforded by the bulky $t$BuMe$_2$Si groups.

Received: March 31, 2003 [Z51519]

**Keywords:** hamigeran B · hydrogenolysis · natural products · silyl groups · total synthesis

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