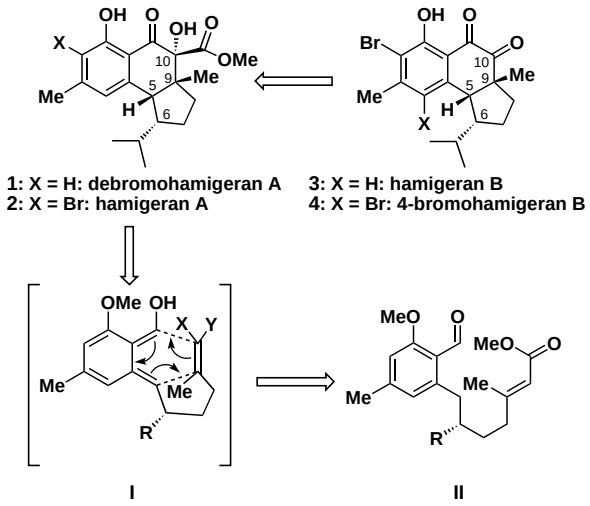
Total Synthesis of Hamigerans: Part 2. Implementation of the Intramolecular Diels–Alder Trapping of Photochemically Generated Hydroxy-*o*-quinodimethanes; Strategy and Completion of the Synthesis**

K. C. Nicolaou,* David Gray, and Jinsung Tae

In the preceding communication,[1] we detailed the development of a suitable methodology for the expedient construction of the benzannulated carbocyclic frameworks of members of the hamigeran class of natural products[2] (e.g. **1**–**4**, Scheme 1) as immediate synthetic targets. Based on the



Scheme 1. Molecular structures of the hamigerans **1**–**4** and retrosynthetic analysis through photo-enolization and intramolecular trapping of reactive hydroxy-*o*-quinodimethane species **I**.

photo-induced generation and trapping of hydroxy-*o*-quinodimethanes **I**, this synthetic technology was the centerpiece of our synthetic strategy towards these biologically active compounds as shown retrosynthetically in Scheme 1. In the same article[1] we also reported the construction of two appropriately functionalized benzaldehydes (e.g. **II**, Scheme 1), which are needed as potential precursors for the total synthesis of the hamigerans. Herein we describe the implementation of this strategy and the completion of the total synthesis of hamigerans A and B (**1**–**4**) and several of their epimers.

[*] Prof. Dr. K. C. Nicolaou, D. Gray, Dr. J. Tae
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

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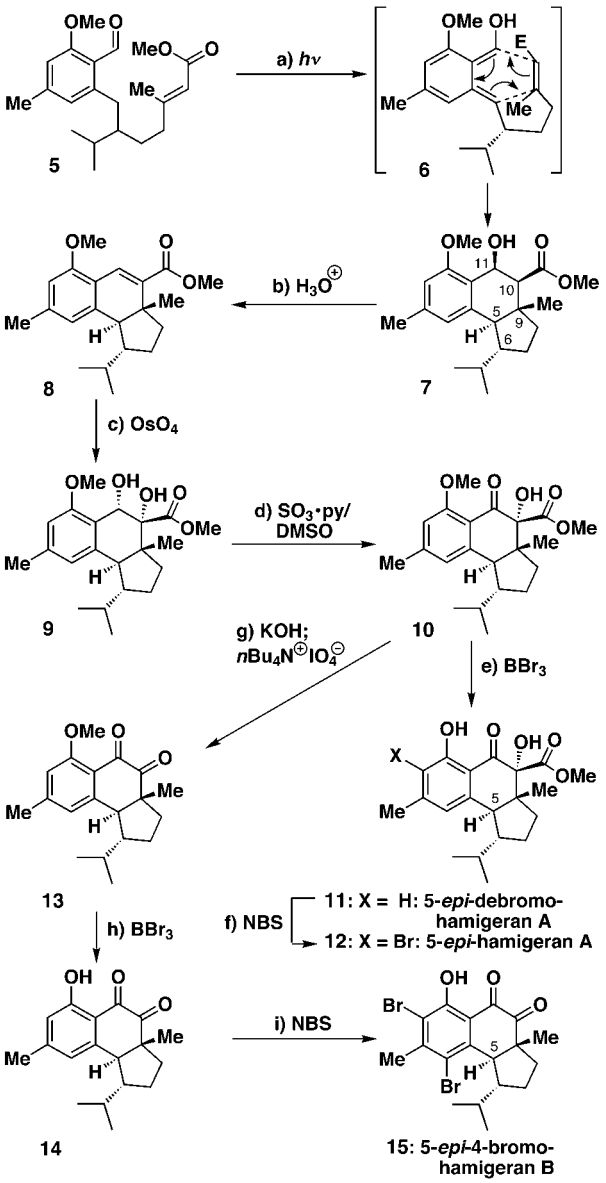
A thorny problem in reaching the hamigeran structure was expected to be the establishment of the relative stereochemistry at the four contiguous stereocenters situated at C5, C6, C9, and C10. At the outset, the most direct approach to solve this problem appeared to be the one initiated from benzaldehyde **5** (Scheme 2). Pleasantly, and as predicted from molecular models, when benzaldehyde **5** was irradiated in deoxygenated benzene solution (450-W Hanovia lamp, pyrex filter) the tricyclic system **7** was obtained in 91% yield, presumably via the transient species **6** (E = COOMe). The relative



Scheme 2. Synthesis of the 5-*epi*-hamigeran series (**11**, **12**, and **15**). Reagents and conditions: a) benzene, *hν* (450-W Hanovia lamp, pyrex filter), 25 °C, 20 min, 91%; b) 1% HCl in MeOH, 60 °C, 30 min, 90%; c) OsO_4 (0.08 equiv), NMO (2.0 equiv), py (2.0 equiv), THF/*t*BuOH/H_2O (10:10:1), 25 °C, 12 h, 93% (ca. 12:1 mixture of two isomers); d) $SO_3 \cdot py$ (3.0 equiv), Et_3N (6.0 equiv), DMSO/CH_2Cl_2 (1:1), 0 °C, 2 h, 88%; e) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 95%; f) NBS (1.05 equiv), iPr_2NH (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 95%; g) KOH, MeOH, 70 °C, 2 h; then nBu_4NIO_4 (2.0 equiv), dioxane, 100 °C, 1 h, 65%; h) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 95%; i) NBS (2.5 equiv), DMF, 0 °C, 3 h, 95%. NMO = 4-methylmorpholine *N*-oxide, py = pyridine, NBS = *N*-bromosuccinimide.

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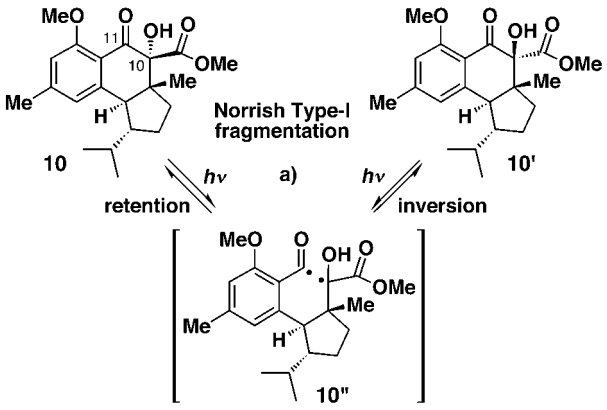
configuration of the substituents on the periphery of the newly formed framework is apparently fully controlled by the single C6 stereocenter of the starting substrate **5**. All the stereocenters in **7** were formed with single stereochemistries, except for the one at C10, which was generated as a mixture of isomers (ca. 3:1 ratio), a consequence of the *E*:*Z* mixture (ca. 3:1) in the starting material **5**. The *trans* relationship between the C6 isopropyl group and the C9 methyl moiety in **7** was particularly crucial for the eventual success, as these were the two permanently set centers. In contrast, the wrongly formed stereochemistry at C5 could, in principle, be corrected by epimerization. As seen from the next step (**7** → **8**, HCl/MeOH, 90% yield) the stereochemistry at C10 and C11 was at this stage inconsequential, since it is removed at least temporarily. This elimination step also converged the two C10 epimers obtained in the cyclization reaction. Dihydroxylation of unsaturated ester **8** with NMO/OsO_4 (for abbreviations of reagents and protecting groups, see legends in schemes) in the presence of pyridine resulted in the formation of the α-dihydroxy compound **9** contaminated with small amounts of its isomer in which dihydroxylation occurred from the β-face (ca. 12:1 ratio, 93% total yield). The benzylic alcohol in **9** was then oxidized with $SO_3 \cdot$ py/DMSO to give hydroxy ketoester **10** in 88% yield. Demethylation of **10** proceeded smoothly upon exposure to BBr_3 at $-78\,^\circ C$ to afford 5-*epi*-debromohamigeran A (**11**) in 95% yield. Attempts to epimerize **11** or any of its precursors **7** – **10** under a variety of conditions failed. Of particular note was the effect of UV irradiation on a benzene solution of hydroxy ketoester **10**: upon irradiation with a UV Hanovia lamp, **10** was converted into an equilibrium mixture of C10 epimers (**10**/**10′** $\approx$ 1:3; see Scheme 3). A likely mechanism for this equilibration is a



Scheme 3. Photo-induced epimerization of hydroxy ketoester **10** at C10 by means of Norrish Type-I fragmentation – recombination. a) 450-W Hanovia lamp, pyrex filter, benzene, ambient temperature, 20 min, 93%, equilibrium mixture of C10 epimers (10/10′ $\approx$ 1:3).

Norrish Type-I homolysis[3, 4] of the C10–C11 bond to form the diradical species **10″**, which then closes with retention of stereochemistry to form **10** again, or with inversion of stereochemistry to form its epimer **10′** (Scheme 3).

With enough quantities of precursor **10** in hand and with future chemical biology studies in mind, we decided to establish procedures for reaching further hamigeran analogues, albeit epimeric at C5. Thus, selective monobromination[5] *ortho* to the phenolic group of **11** (Scheme 2) was smoothly effected by the action of NBS and catalytic amounts of $i Pr_2NH$ in CH_2Cl_2 at $0\,^\circ C$, to furnish 5-*epi*-hamigeran A (**12**) in 95% yield. It was also found that basic hydrolysis of ester **10** (KOH/MeOH), followed by oxidative 1,2-cleavage promoted by $n Bu_4NIO_4$ in dioxane[6] offers a practical entry into the hamigeran B series. Thus, diketone **13** was obtained from **10** in 65% overall yield and was subsequently demethylated (BBr_3, $-78\,^\circ C$, 95% yield) to afford phenolic diketone **14**. Aromatic bromination of **14** (NBS, DMF) provided 5-*epi*-4-bromohamigeran B (**15**) in 95% yield (for selected data, see Table 1).

Table 1. Selected data for compounds **15** and **34**.

15: colorless syrup; $R_f = 0.5$ (silica gel, hexane/EtOAc 4:1); IR (film): $\tilde{\nu}_{max} = 2959$, 1734, 1633, 1455, 1376, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 13.1$ (s, 1H), 3.29 (d, $J = 10.8$ Hz, 1H), 2.78 (s, 3H), 2.25 (m, 1H), 1.99 (m, 1H), 1.95 – 1.85 (m, 2H), 1.67 – 1.60 (m, 2H), 1.13 (s, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.80 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 196.9$, 185.5, 160.8, 150.8, 141.2, 119.0, 114.3, 114.0, 57.9, 52.6, 41.1, 31.7, 29.8, 27.2, 22.1, 21.1, 19.2, 14.5; HR-MS (MALDI): calcd for $C_{18}H_{20}Br_2O_3$ [M+Na^+]: 464.9671; found: 464.9659

34: colorless solid; $R_f = 0.5$ (silica gel, hexane/EtOAc 1:1); $[\alpha]_D^{22} = +38.8$ ($c = 0.100$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3437$, 2857, 1738, 1692, 1604, 1460, 1222, 1083, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 6.72$ (s, 1H), 6.61 (s, 1H), 4.80 (s, 1H), 3.86 (s, 3H), 3.54 (d, $J = 5.9$ Hz, 1H), 3.50 (s, 3H), 2.37 (s, 3H), 1.95 (m, 1H), 1.70 (dd, $J = 14.8$, 8.9 Hz, 1H), 1.58 – 1.41 (m, 2H), 1.39 (s, 3H), 1.37 – 1.22 (m, 2H), 1.16 (d, $J = 6.2$ Hz, 3H), 0.72 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 192.1$, 169.9, 158.6, 146.1, 145.7, 122.4, 117.3, 109.7, 84.1, 55.9, 53.1, 52.4, 51.3, 46.7, 34.3, 26.9, 26.8, 24.6, 23.5, 22.6, 21.7; HR-MS (MALDI): calcd for $C_{21}H_{28}O_5$ [M+Na^+]: 383.1829; found: 383.1817.

Our next attempt at the total synthesis of the hamigerans involved the use of a second benzaldehyde (**16**, Scheme 4), which incorporated an oxygen functionality at C6 in the hope that this additional handle might provide the necessary activation for the obligatory epimerization at C5. Furthermore, since this aldehyde was obtained by asymmetric synthesis, as described in the preceding paper,[1] this new strategy was expected to provide an enantioselective route to the targeted compounds. Thus, photo-irradiation of **16** ($E/Z \approx 3{:}1$, inconsequential) under the standard conditions already described for **5** led to the tricyclic hydroxy ester **17** in 92% yield and as a mixture of C10 epimers (ca. 3:1, major product shown, inconsequential). The heating of **17** in methanolic HCl at $60\,^\circ C$ affected both the dehydration and MOM cleavage, leading to hydroxy unsaturated ester **18** in 91% yield. This sequence allowed the multigram synthesis of intermediate **18** with $>99\%$ enantiomeric purity as determined by chiral HPLC. The olefin **18** was then stereoselectively dihydroxylated by following the already established protocol (see above) to yield triol **19** as the major product in 91% yield (ca. 12:1 ratio of two separable isomers).

Selective protection of the vicinal hydroxy groups in **19** with 2-methoxypropene and catalytic amounts of PPTS followed by Dess – Martin oxidation of the remaining hydroxy group gave the corresponding ketone acetonide **21**. With the

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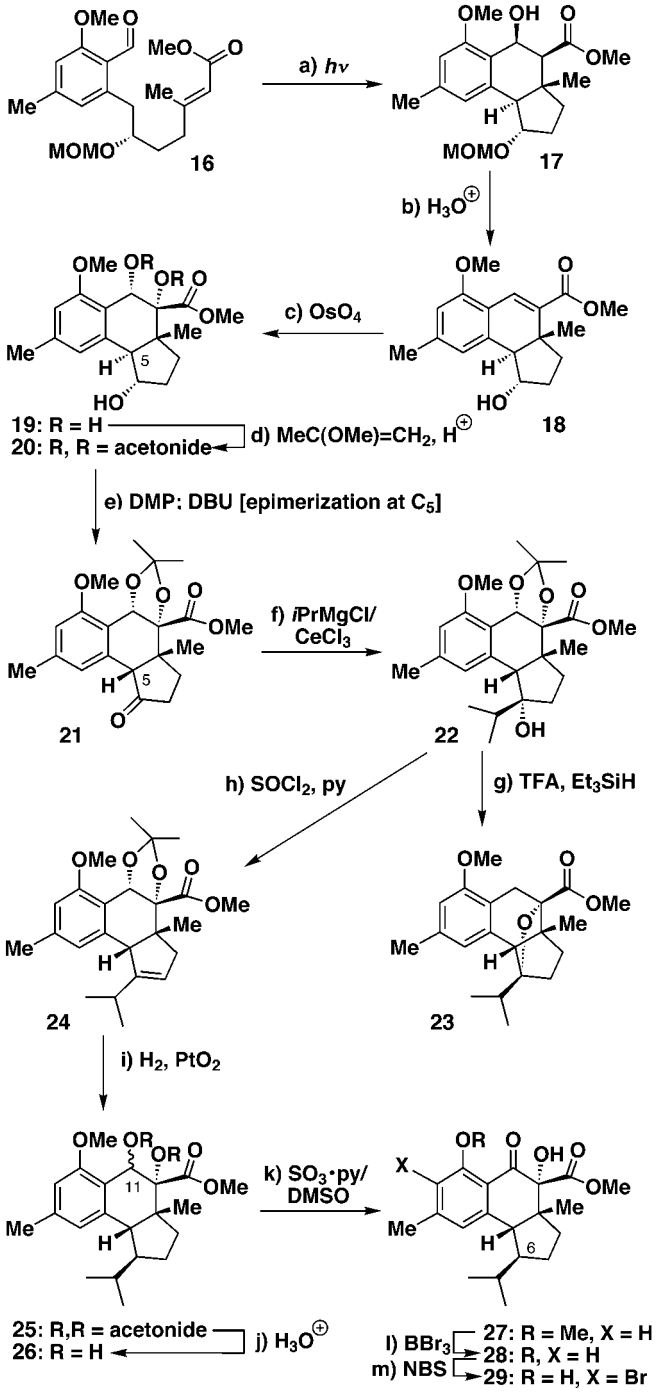

Scheme 4. Synthesis of the 6-*epi*-hamigeran series (**28** and **29**). Reagents and conditions: a) benzene, *hν* (450-W Hanovia lamp, pyrex filter), 25 °C, 20 min, 92 %; b) 1 % HCl in MeOH, 60 °C, 30 min, 91 %; c) OsO_4 (0.08 equiv), NMO (2.0 equiv), py (2.0 equiv), THF/*t*BuOH/H_2O (10:10:1), 25 °C, 12 h, 91 % (ca. 12:1 mixture of isomers); d) 2-methoxypropene, PPTS (0.5 equiv), CH_2Cl_2, 0 °C, 30 min, 93 %; e) DMP (2.0 equiv), CH_2Cl_2, 0 °C, 1 h; then DBU (0.3 equiv), CH_2Cl_2, 0 °C, 10 min, 92 %; f) *i*PrMgCl (2.0 equiv), $CeCl_3$ (2.0 equiv), −78 → 0 °C, 1 h, 95 %; g) TFA (20 equiv), Et_3SiH (50 equiv), CH_2Cl_2, 25 °C, 1 h, 65 %; h) $SOCl_2$ (8.0 equiv), py, CH_2Cl_2, −60 °C, 15 min, 94 % (10:2:1 mixture of three isomers); i) PtO_2 (0.2 equiv), H_2 (3 atm), EtOH, 25 °C, 2 h, 94 % (ca. 3:1 mixture of C6 epimers); j) HCl (3 N)/THF (1:1), 80 °C, 4 h, 70 % (ca. 1.3:1 mixture of C11 epimers); k) $SO_3 \cdot$ py (3.0 equiv), Et_3N (6.0 equiv), DMSO/CH_2Cl_2 (1:1), 0 °C, 2 h, 82 %; l) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 95 %; m) NBS (1.05 equiv), *i*Pr_2NH (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 95 %. PPTS = pyridinium *p*-toluenesulfonate, DMP = Dess–Martin periodinane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFA = trifluoroacetic acid.

neighboring carbonyl group in place, base-induced isomerization at C5 proved extremely facile, requiring only a ten-minute exposure to DBU at 0 °C to afford the desired product **21** with the *cis* 5,6 junction (86 % yield over three steps). The carbonyl group also served its second purpose as an electrophile well, allowing the cerium-mediated introduction of the required isopropyl group (**21** → **22**), and thus marking our arrival at intermediate **22** (exclusive attack from the *exo* face, 95 % yield). An attempt to reductively remove the tertiary alcohol group from **22** by treatment with TFA/Et_3SiH led, remarkably, to the polycyclic ether **23** (65 % yield), presumably formed by trapping the incipient tertiary carbonium ion with the proximal C10 oxygen atom, and reductive cleavage of the benzylic C–O bond.

Having experienced similar side reactions under various other conditions, we opted to proceed through olefin **24**, which was readily obtained from alcohol **22** by the action of $SOCl_2$/py (−60 °C, 94 % yield) as an inseparable mixture with its conjugated (**24′**) and exocyclic (**24″**) double bond isomers (not shown, ≈10:2:1 ratio). However, the intended reduction of this olefin to furnish the correct stereochemistry of the hamigerans at C6 as expected from an *exo* face attack (compare addition of isopropyl group to the carbonyl function, step **21** → **22**) proved elusive. In various reduction experiments, the suspected incorrect C6 stereoisomer **25** was contaminated by unreactive tetrasubstituted olefinic isomers **24′** and **24″**, thus plaguing this approach with further complications. Therefore, it was decided to change course. But before that, and as in the previous case (C5-*epi* compounds), we moved to complete the synthesis of the new series of hamigeran analogues attainable from **24**. Thus, acid-induced hydrolysis of the acetonide group from the reduction product **25** with HCl (3 N)/THF (1:1) at 80 °C led to diol **26** (mixture of C11 epimers, ca. 1.3:1 ratio), whose chromatographic purification and spectroscopic characterization now became possible. The mixture of benzylic alcohols **26** was then oxidized with $SO_3 \cdot$ py/DMSO to afford hydroxy ketoester **27** in 82 % yield and as a single stereoisomer. Demethylation of **27** (BBr_3, −78 °C, 95 % yield) led to phenol **28**, whose proton NMR spectroscopic analysis (NOE) confirmed that, indeed, the isopropyl group had the incorrect stereochemistry (C6) and that compound **28** was 6-*epi*-debromohamigeran A. This compound was smoothly converted into 6-*epi*-hamigeran A (**29**) by exposure to stoichiometric amounts of NBS in the presence of *i*Pr_2NH (95 % yield).

In the face of this new failure to establish the correct C6 stereochemistry, we began to search for a new branching sequence from one of our readily available intermediates. Such a path was finally found starting with olefin **24** as shown in Scheme 5. The crucial observation for this sequence was made when olefin **24** was hydroborated with $BH_3 \cdot Me_2S$ under sonication conditions to give, upon oxidative workup, the desired 6*R*,7*R* alcohol isomer **30** as the major product (*exo* addition, 44 % yield) together with its α-stereoisomer (*endo* addition, 24 % yield). The chromatographically separated isomer **30** was then sequentially converted (PhOC(S)Cl/py) into the phenylthionocarbonate (**31**, 85 % yield) and then into the deoxygenated product **32** by heating with *n*Bu_3SnH/AIBN

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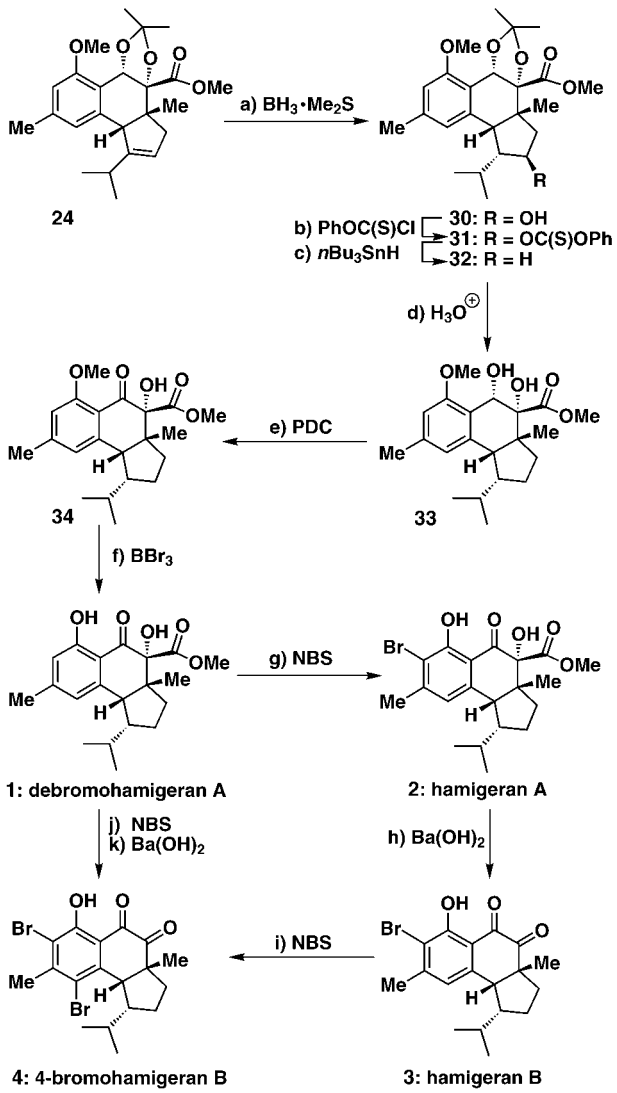
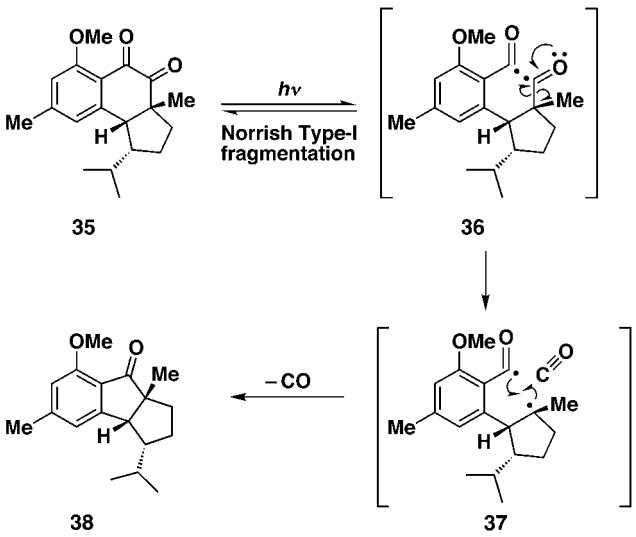


Scheme 5. Total synthesis of hamigerans A (**1**,**2**) and B (**3**,**4**). Reagents and conditions: a) $BH_3 \cdot Me_2S$ (40 equiv), THF, sonication, 40 °C, 8 h, 68 % (ca. 1.8:1 mixture of two isomers); b) PhOC(S)Cl (2.0 equiv), py, 25 °C, 2 h, 85 %; c) nBu_3SnH (8.0 equiv), AIBN (0.2 equiv), benzene, reflux, 1.5 h, 75 %; d) HCl (1N), THF/H_2O (1:1), 80 °C, 1 h, 88 %; e) PDC (2.5 equiv), 4 Å molecular sieves, CH_2Cl_2, 25 °C, 3 h, 83 %; f) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 95 %; g) NBS (1.05 equiv), iPr_2NH (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 95 %; h) $Ba(OH)_2$ (15 equiv), MeOH/H_2O (2:1), air, 25 °C, 2 h, 82 %; i) NBS (1.5 equiv), DMF, 25 °C, 1 h, 95 %; j) NBS (3.0 equiv), DMF, 25 °C, 1 h, 95 %; k) same procedure as step h above, 65 %. AIBN = azobisisobutyronitrile, PDC = pyridinium dichromate.

(benzene, reflux, 75 % yield). Formation of intermediate **32** paved the way for the completion of the synthesis of all four targeted natural products. Thus, the acetonide protecting group was removed from **32** by heating at 80 °C with HCl (1N) in THF (1:1) to afford diol **33** in 88 % yield. Although the standard $SO_3 \cdot$py/DMSO protocol for the oxidation of the benzylic position gave low yields, PDC succeeded admirably in converting **33** into **34** (83 % yield; for selected data, see Table 1). The first natural product in this series, debromohamigeran A (**1**), was generated from **34** (95 % yield) by the BBr_3-induced cleavage protocol employed above for the *epi* series, whereas the second product, hamigeran A (**2**), was obtained from the NBS-mediated bromination (95 % yield) of debromohamigeran A (**1**). An expedient conversion of hamigeran A (**2**) into hamigeran B (**3**) was devised based on a cascade reaction initiated by $Ba(OH)_2$ in MeOH/H_2O (2:1) under aerobic conditions involving: a) saponification; b) decarboxylation; and c) auto-oxidation (82 % overall yield). Finally, 4-bromohamigeran B (**4**) was generated from hamigeran B (**3**) by NBS-facilitated introduction of the second bromine atom (95 % yield). 4-Bromohamigeran B (**4**) could also be obtained from **1** by dibromination (NBS, DMF) followed by treatment with $Ba(OH)_2$ (65 % overall yield). The spectroscopic data for all four synthetic hamigerans **1**–**4** matched those reported for the naturally derived compounds.[2]

An interesting observation made during this study is worth mentioning, particularly since it considerably expands the scope of the developed hydroxy-*o*-quinodimethane based technology. Thus, in our attempts to convert compound **34** (Scheme 5) into the C10,C11-diketone system **35** (Scheme 6) by the two-step protocol used in the conversion of **10** → **13** (Scheme 2; a) KOH; b) nBu_4NIO_4), we observed considerable amounts of a by-product whose structure was determined to be **38** (Scheme 6). It was subsequently confirmed that this ring contraction process could be accelerated by UV irradiation, thus becoming a synthetically useful reaction under these conditions (**35** → **38**, 90 % yield, Scheme 6). Presumably the



Scheme 6. Proposed mechanism for the photo-induced decomposition of **35** to form **38**.

Norrish Type-I mechanism shown in Scheme 6 operates in this transformation. The potential of this ring contraction process in organic synthesis is under further investigation.

The chemistry described herein and in the preceding communication[1] demonstrates the power of the inter- and intramolecular trapping of photochemically generated hydroxy-*o*-quinodimethanes in complex molecule construction. Furthermore, the reported expedient and efficient total syntheses of the hamigerans and their analogues are expected to facilitate chemical biology investigations of these scarce,[7] and therefore, little-studied marine natural products.

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[7] We thank Professor P. S. Rutledge and Professor R. C. Cambie for informing us about the scarcity of these compounds. Apparently the small amounts of the originally isolated compounds have now been exhausted.

The Influence of Excess Ammonia on the Mechanism of the Reaction of Boron Trichloride with Ammonia—An Ab Initio Molecular Dynamics Study**

Silke Reinhardt, Christel M. Marian,* and Irmgard Frank

The reaction of boron trichloride with ammonia is well known. Already in 1921, BN was produced by ammonolysis of boron trichloride in liquid ammonia and subsequent heating of the primary products.[1] Today, the reaction of BCl_3 with NH_3 is used for the preparation of hexagonal and amorphous boron nitride by means of chemical vapor deposition (CVD).[2]

To shine light on the processes during the CVD of BN, Reinhardt et al. recently investigated the energetic course of the gas-phase reaction of BCl_3 with NH_3.[3] They were able to show that the substitution of the first chlorine atom of BCl_3 in the gas phase is a two-step reaction (Figure 1): the formation of an $NH_3 \cdot BCl_3$ adduct in the first step is followed by the elimination of hydrogen chloride to yield aminodichloroborane. The elimination requires the surmounting of a barrier of 25 kJ mol^{-1} with respect to the reactants, or 151 kJ mol^{-1} relative to the adduct. The second and third substitutions follow the same mechanism. The reaction barriers become lower with decreasing chlorine content, and the heats of reaction become smaller. As a result of its high-lying transition state, the first chlorine substitution is the rate-determining step, and the reaction that yields BN is expected to proceed only at elevated temperatures. However, the ammonolysis of BCl_3 is known to occur spontaneously in the condensed phase even at low temperatures and to be very exothermic.[1] It can therefore be concluded that additional NH_3 molecules strongly affect the energetic course and the mechanism of the reaction.

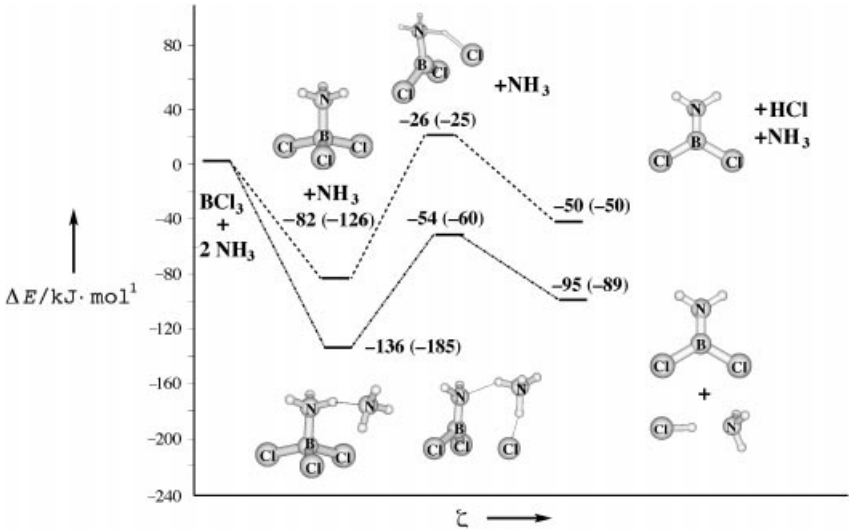

Figure 1. Energy course of the gas-phase reaction of boron trichloride with one ammonia molecule (top curve) and two ammonia molecules (bottom curve), determined at the BLYP level of theory (RI-MP2 values are given in parentheses). ζ = Reaction coordinate.

The aim of the work herein is to study the influence of additional ammonia molecules on the mechanism and on the energy profile of the first chlorine substitution by an amino group. According to the results of time-independent RI-MP2 calculations (see Calculation Methods), the barrier of the gas phase reaction is lowered in the presence of another NH_3 molecule owing to the formation of a six-centered transition state (Figure 1). However, with respect to the $H_3N \cdot BCl_3$ adduct the barrier is still rather high (125 kJ mol^{-1}). Furthermore, the product side of the reaction is only slightly stabilized by a single NH_3 molecule. Because solvent molecules participate actively in the reaction, the influence of excess NH_3 cannot be simulated by means of a continuum

[*] Priv.-Doz. Dr. C. M. Marian
GMD Forschungszentrum Informationstechnik GmbH
Institut für Algorithmen und Wissenschaftliches Rechnen (SCAI)
Schloss Birlinghoven, 53754 St. Augustin (Germany)
Fax: (+49) 2241-14-2656
E-mail: christel.marian@gmd.de
S. Reinhardt
Institut für Physikalische und Theoretische Chemie
Universität Bonn
Wegelerstrasse 12, 53115 Bonn (Germany)
Dr. I. Frank
Institut für Physikalische Chemie
Ludwig-Maximilians-Universität
Butenandtstrasse 5 – 13, 81377 München (Germany)

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