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Synthesis of the hamigeran skeleton through an electro-oxidative coupling reaction

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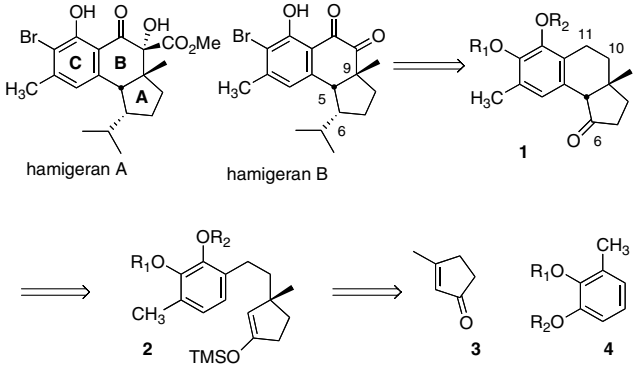
Abstract—The tricyclic core of the hamigerans has been prepared through the use of a two-step electrochemical benzannulation reaction. The annulation proceeds through an initial conjugate addition of a phenethyl cuprate to 3-methylcyclopentenone with in situ silylation of the resulting enolate. Anodic oxidation effectively couples the pendant arene and the silyl enolether to produce a key intermediate for the synthesis of the natural products. Careful optimization revealed that the use of 'alcohol-free' conditions during the electrolysis was critical to obtain high yields of the annulated product. This method allowed the preparation of the tricyclic core of hamigeran A and B in just four steps from commercially available starting materials.

The hamigerans are unusual halogenated marine natural products isolated by Cambie and co-workers[1] in 2000 from a sponge harvested near New Zealand. Of particular note was the biological activity of hamigeran B, which showed potent inhibition of both the polio and herpes virus while displaying relatively little cytotoxicity. Hamigeran B has been synthesized by Nicolaou and co-workers[2] using a novel photochemical benzannulation reaction, Clive and Wang[3] who used a free radical process to annulate the five membered A-ring onto a tetralone derivative and Trost et al.[4] through a palladium catalyzed coupling strategy. Mehta and Shende[5] has synthesized 6-*epi*-hamigeran B through the use of a key Heck cyclization.

Over the past several years, we have been developing methodology for the construction of annulated arenes (most notably furans) through the electro-oxidative coupling of silyl enolethers and pendant aromatic nucleophiles.[6] The pioneering work of Moeller and co-workers[7] and others[8] has shown that electron-rich aromatics and olefins can be oxidatively coupled under electrochemical conditions. This type of reaction forms the basis for our two-step annulation protocol, which involves the silyl-promoted addition of a cuprate bearing a pendant arene to an enone followed by anodic oxidation to couple the two electron rich moieties. These reactions proceed under kinetic control and lead exclusively to the formation of *cis*-fused products. Although the majority of our work has centered upon the use of furan as the terminator, we have been interested in extending this process to other aromatics, notably benzenoid systems. The structure and biological activity of the hamigerans make them an appealing target for this annulation methodology (Scheme 1).

We hoped to access both hamigeran A and B, as well as analogs, from the tricyclic ketone **1**, which would be



Scheme 1. Approach to the hamigerans based on an arene–enolether coupling.

Keywords: Electrochemistry; Anodic oxidation; Hamigeran; Annulation.
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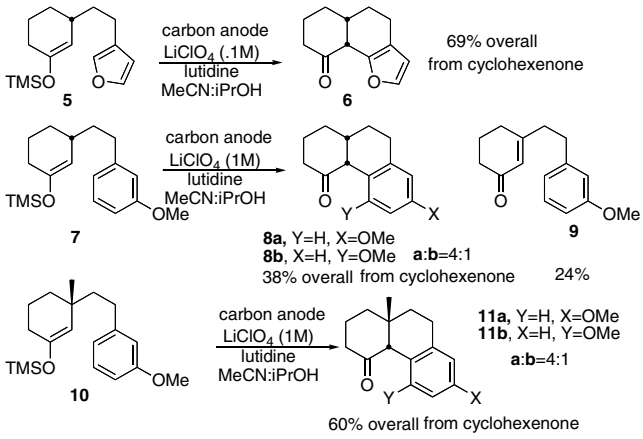
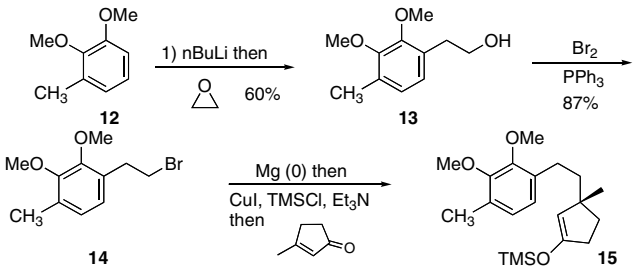


Scheme 2. Model cyclizations.



Scheme 3. Synthesis of a cyclization precursor.

available from the electro-oxidative annulation strategy. A carbonyl group at C6 will allow introduction of the A-ring isopropyl group while C10 and C11 will be retained in reduced form. It is anticipated that sequential oxidation of the benzylic C11 position followed by oxidation at C10 can be used to introduce the remaining B-ring functionality. The *cis* relationship at C4 and C9 of the key intermediate will be a consequence of the kinetically controlled electrochemical cyclization of **2**, a direct precursor to the key tricyclic intermediate. This compound is envisioned to arrive from simple A-ring and C-ring subunits such as **3** and **4**. Preliminary work on model cyclizations of this type had shown that, despite the similarities, the use of an aromatic terminator in this case was distinctly different from the furanoid case (Scheme 2).

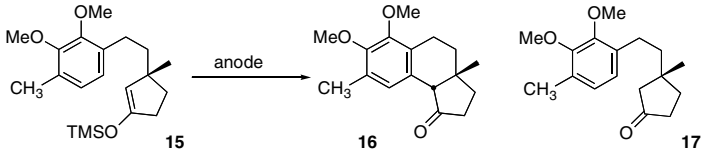
The closure of the corresponding benzenoid substrate **7** under the conditions[6c] used successfully for the furan-based closure (**5**→**6**) was a very poor process and produced only trace amounts of the cyclized ketones **8a/b**. The major product **9** was derived from the loss of a proton from the initially generated radical-cation. A methyl group at the β-position eliminated this pathway, although the yields of the ring closure were still significantly lower than the furan case. We attributed this rather poor cyclization reaction to the lower nucleophilicity of the anisyl group relative to the furyl appendage. However, a significant improvement in yield was found when the concentration of the supporting electrolyte ($LiClO_4$) was increased 10-fold to a concentration of 1 M. Under these conditions, a good ring closure could be observed as long as the competing elimination was blocked (**10**→**11a/b**). Referring back to the synthetic plan for the hamigerans, we were optimistic that the electrochemical ring closure would be a useful process for constructing this system (Scheme 3).

Not only was a β-substituent present to block elimination, but this synthesis would call for the use of a catechol-based nucleophile, which was expected to close at a faster rate than the simple anisyl derivatives. The aromatic A-ring fragment was easily prepared from commercially available 3-methylcatechol by directed *ortho* metalation followed by a quench of the anion with ethylene oxide. Conversion of the phenethyl alcohol **13** to the corresponding bromide **14** was accomplished under standard conditions with bromine and triphenylphosphine. Preparation of the Grignard reagent from the bromide and conversion to the corresponding cuprate preceded trimethylsilyl chloride-accelerated addition to 3-methylcyclopentenone. The resultant silyl enolether **15** was isolated and used in the subsequent electrochemical reaction without the benefit of further purification (Table 1).

Disappointingly, attempts to close the B-ring of the hamigerans under our previously optimized conditions (entry 1) resulted only in poor yields of the cyclized ketone **16**. The major by-product identified was the hydrolyzed ketone **17**, a type of side reaction not previously observed in these closures. In previous optimization studies, variables such as electrolyte composition and concentration, current density and electrode material were found to be critical for the facility of the electrolysis. Returning to the original conditions reported for the furan case showed again the importance of electrolyte concentration (entry 2). Increasing the concentration of $LiClO_4$ to 2 M (the practical upper limit set by the solubility of the salt in *i*-PrOH/MeCN) led to an increase in yield, but the viscous nature of the solution made effective mixing and work-up difficult and was not viewed as practical. The role of the higher electrolyte concentration in this type of cyclization remains unclear but it may relate to the ability of the more polar solution to stabilize the radical-cation intermediate and allow the slower cyclization reaction to be competitive with other reactions. Changes in electrolyte, electrode composition and current density had only deleterious effects on the cyclization (entries 4–10).

The lower overall yields in this system as compared to **10** were surprising, as it was believed that the presence of additional donors on the aromatic would accelerate the cyclization reaction. In every case where cyclized product was formed, significant quantities of the hydrolysis product **17** were observed as the major by-product. Previous work in the furan series had shown that the silyl enolethers were unstable toward methanol but that the bulkier 2-propanol was compatible with this functionality. A control experiment showed that silyl enolether **15** was stable to the isopropanol/acetonitrile solution for extended periods of time and that conversion to ketone **17** only took place during the electrolysis reaction. Alcohol additives have always been used in

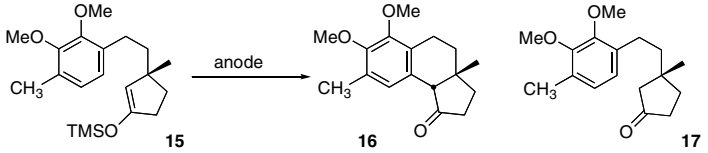
Table 1. Electrochemical cyclization studies



Entry	Anode[a]	Electrolyte	Electrolyte concn (M)	Current density[b]	Yield[c] (%) **16**	Ratio[d] **16**:**17**
1	Carbon	$LiClO_4$	1	1	32	3.1:1
2	Carbon	$LiClO_4$	0.1	1	0	0:1
3	Carbon	$LiClO_4$	2	1	35	3.6:1
4	Carbon	*n*-Bu_4ClO_4	0.1	1	0	0:1
5	Carbon	*n*-Bu_4ClO_4	1	1	0	0:1
6	Carbon	$LiNTf_2$	1	1	Trace	~0:1
7	RVC	$LiClO_4$	1	N/A	<5	5:95
8	Pt	$LiClO_4$	1	N/A	0	N/A
9	Carbon	$LiClO_4$	1	0.1	0	0:1
10	Carbon	$LiClO_4$	1	0.5	5	~0:1

[a] All reactions run at a concentration of 0.02 M in MeCN/*i*-PrOH (4:1).
[b] Reported in mA/cm^2.
[c] Two-step yield from 3-methylcyclopentenone.
[d] Determined by GC–MS.

Table 2. Effect of alcohol concentration on electrochemical cyclization



Entry[a]	Ratio *i*-PrOH/MeCN	Current density[b]	Yield[c] (%) **16**	Ratio **16**:**17**[d]
1	1:4	1	32	3.1:1
2	0:1	1	57	5.8:1
3	0:1	0.5	67	6.5:1
4	0:1	0.3	44	4.4:1

[a] All reactions run at a concentration of 0.02 M with a carbon anode.
[b] Reported in mA/cm^2.
[c] Two-step yield from 3-methylcyclopentenone.
[d] Ratio determined by GC–MS.

these types of reactions[7] as both a cation scavenger and as the cathodic component, where it is reduced to an alkoxide that could likely be responsible for the formation of **17**. We varied the amount of alcohol in an attempt to suppress this unwanted side reaction (Table 2).

Surprisingly, it was observed that the alcohol additive could be eliminated from the reaction altogether (entry 2) and that significantly improved yields of the cyclized product could be realized at the expense of hydrolysis. A combination of a lower current density and alcohol-free conditions gave a reliable 65–68% yield overall for two steps from 3-methylcyclopentenone (entry 4); formed exclusively as the desired *cis*-isomer.[9]

A key tricyclic intermediate en route to the synthesis of hamigeran A and B has been prepared in four steps from dimethoxytoluene. The route features a key electrochemical annulation reaction under alcohol-free conditions and complements our methodology using furyl terminators. The conversion of this intermediate to the hamigerans will be reported in due course.

Acknowledgements

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References and notes

1. (a) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79; (b) Cambie, R. C.; Rickard, C. E. F.; Rutledge, P. S.; Wellington, K. D. *Acta Cryst. C* **2001**, *57*, 958.
2. (a) Nicolaou, K. C.; Gray, D.; Tae, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675; (b) Nicolaou, K. C.; Gray, D.; Tae, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3679.
3. (a) Clive, D. L. J.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 7731; (b) Clive, D. L. J.; Wang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3406.
4. Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480.
5. Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049.
6. (a) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535;

(b) Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Wright, D. L. *Org. Lett.* **2002**, *4*, 3763; (c) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, 3726.

7. (a) Moeller, K. D.; New, D. G. *Tetrahedron Lett.* **1994**, *35*, 2857; (b) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578.
8. For a comprehensive review see: Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527–9554.
9. To a 250 mL beaker charged with 70 mL of CH_3CN, 7.62 g of $LiClO_4$, and 0.67 mL of 2,6-lutidine was placed the crude silyl enol ether (500 mg, 1.43 mmol). The solution was degassed by sonication prior to electrolysis. An electrode consisting of alternating stainless steel and carbon plates was submerged into the solution and 10 mA of current was passed until 2.2 F/mol were consumed. The electrodes were removed and the solution cooled to −5 °C to facilitate the precipitation of most of the $LiClO_4$. The mother liquor was decanted and the salt was washed with cold diethyl ether (2×75 mL). The combined organic fractions were concentrated in vacuo and taken up in 100 mL of diethyl ether. The ether layer was washed with 1 M HCl, water, satd $NaHCO_3$, and brine. After drying over Na_2SO_4, the organic layer was concentrated and purified by flash chromatography (20:1 hexanes/EtOAc) to yield ketone (**16**) (263 mg, 67%) as a viscous, colorless oil. IR (neat) 2931, 2856, 1741, 1606, 1573, 1484, 1454 cm^{-1}; ^1H NMR (500 mHz, $CDCl_3$): δ 6.88 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.85 (s, 1H), 2.80 (dd, J = 5.6 Hz, 3.2 Hz, 1H), 2.61–2.68 (m, 1H), 2.37–2.45 (m, 2H), 2.28 (s, 3H), 1.93–1.98 (m, 1H), 1.83–1.88 (m, 1H), 1.56–1.62 (m, 1H), 1.50–1.58 (m, 1H), 1.19 (s, 3H); ^{13}C δ 217.1, 150.5, 150.0, 129.9, 128.2, 127.2, 126.5, 60.1, 59.4, 38.0, 37.0, 35.4, 34.2, 30.3, 25.2, 20.2, 16.1; HRMS *m/z* calculated for $C_{11}H_{22}O_3$ (M^+): 274.1569, found: 274.1567.