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An Approach to the Total Synthesis of the Marine Ascidian Metabolite Perophoramidine via a Halogen-Selective Tandem Heck/Carbonylation Strategy

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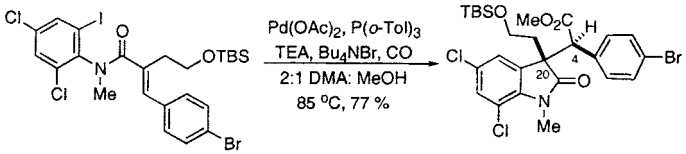
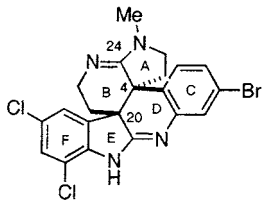
ABSTRACT

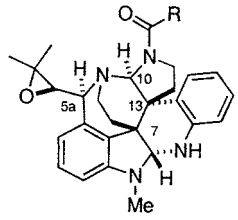


A halogen-selective tandem intramolecular Heck/carbonylation reaction has been developed for the construction of the C,E,F-ring system and the C20 quaternary center found in perophoramidine (1). This process can be effected in good yields in the presence of both the chlorine and bromine atoms found in the natural product. In addition, it is possible to introduce the quaternary center at C4 in a stereoselective manner by a lactone enolate alkylation, using NaH and allyl bromide.

Marine ascidians are a rich source of diverse natural products that display a wide range of biological activity. A recent investigation of the Philippine ascidian *Perophora namei* by Ireland and co-workers resulted in the isolation of the metabolite perophoramidine (**1**).[1] With use of ^{1}H and ^{13}C NMR correlation experiments, a hexacyclic framework containing three halogens, two amidine moieties, and two adjacent quaternary centers was elucidated for the natural product. Interestingly, perophoramidine (**1**) is structurally similar to the previously reported communesin A (**2**) and B (**3**).[2−4] However, the relative stereochemical relationship is reversed between the two quaternary centers at C4,C20 for perophoramidine (**1**) and C7,C13 for **2** and **3**. A preliminary biological assay of **1** showed it to possess moderate cytotoxicity against the human carcinoma cell line HCT116 (IC_{50} = 60 μM). The inherent difficulties in constructing two adjacent quaternary centers and a functionally complex ring

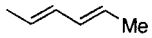


perophoramidine (**1**)



communesin A (**2**) R = Me

communesin B (**3**)

R = 

(1) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124.

(2) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355.

(3) Recently, Hemscheidt and co-workers reported isolation of nomofungin, whose structure was misassigned and which proved to be identical to communesin B (**2**). (a) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J Org. Chem.* **2001**, *66*, 8717. (b) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J Org. Chem.* **2003**, *68*, 1640.

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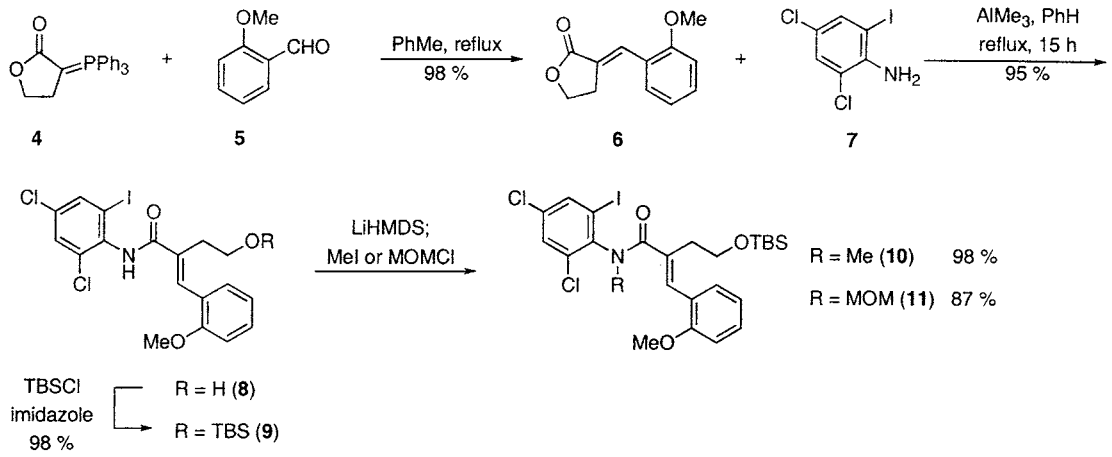
Scheme 1



system like that found in perophoramidine makes it a challenging synthetic target. In this Letter we report our efforts toward a total synthesis of perophoramidine (**1**) via a key halogen-selective tandem intramolecular Heck/carbonylation sequence for the efficient construction of the C20 quaternary center and the C,E,F-ring system.

The Heck reaction has proven to be a powerful tool for the coupling of aryl and vinyl halides with a variety of olefins.[5] In particular, Overman has extensively used the intramolecular Heck reaction[6] as a means to construct quaternary centers and to control absolute stereochemistry in such systems.[7] Recently, tandem intramolecular Heck reactions have been developed by removing the opportunity for β-hydride elimination and thus the resulting palladium intermediate can undergo subsequent coupling with organostannanes, organoboronates, or carbon monoxide providing entry to highly functionalized systems.[8] Our synthetic strategy for perophoramidine is based on effecting a tandem Heck/carbonylation reaction in the presence of the halogens found in **1**. Although one would expect that oxidative insertion of palladium into an aryl iodine bond would be faster than that into aryl chlorine or bromine bonds, we were unable to find any examples of an intramolecular Heck reaction with this type of internal competition where different types of halogens are present in the same molecule.[9] In addition, we needed to test the compatibility of a C ring *ortho* substituent with our key transformation, and to investigate the introduction of the second quaternary center at C4 with the requisite stereochemistry.

We began our study by attempting a Heck/carbonylation reaction in the presence of the two chlorines needed for the F ring of **1** and an *ortho* C-ring methoxy substituent.[10] Synthesis of two Heck precursors was initiated by a stereoselective Wittig olefination between the known γ-lactone ylide[11] **4** and *o*-anisaldehyde (**5**) to afford the methoxybenzylidene lactone **6** in 98% yield exclusively as the *E* isomer (Scheme 1).[12] Ring opening of the lactone **6** with the aluminum amide[13] derived from commercially available 2,4-dichloro-6-iodoaniline (**7**) proceeded smoothly to give the iodo acrylamide **8** in 95% yield. The primary alcohol functionality of iodo acrylamide **8** was then converted to the TBS ether **9** in 98% yield. The iodo amide **9** was *N*-alkylated with MeI to give iodo *N*-methyl amide **10** and, to have a removable protecting group, with MOMCl to give iodo *N*-MOM amide **11** in good yields.

The key tandem Heck/carbonylation reaction was explored by using $Pd(OAc)_2$ as a palladium source, P(*o*-Tol)$_3$ as a ligand, Bu_4NBr as an additive, and triethylamine as the base.

(4) For a biogenetically patterned approach to the communesins, see: May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203.

(5) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 4, p 833. (c) Beletskaya, I. D.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (d) Whitecombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (e) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305. (f) Amatore, C.; Jutard, A. *J. Organomet. Chem.* **1999**, *576*, 254.

(6) For a recent review of the intramolecular Heck reaction, see: Link, J. T. *Org. React.* **2002**, *60*, 157.

(7) (a) Oestrich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *48*, 1439. (b) Ashimori, A.; Overman, L. E. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 718. (c) Asimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **2000**, *122*, 192. (d) Link, J. T.; Overman, L. E. *CHEMTECH* **1998**, *28*, 19. (e) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (f) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488. (g) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

(8) (a) Grigg, R.; Millington, E. L.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605. (b) Brown, S.; Clarkson, S.; Grigg, R.; Thomas, W. A.; Sridharan, V.; Wilson, D. M. *Tetrahedron* **2001**, *57*, 1347. (c) Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 1361. (d) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88. (e) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (f) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919.

(9) For a halogen-selective intermolecular Suzuki−Miyaura coupling involving 1-bromo-3-chloro-5-iodobenzene, see: Hensel, V.; Schluter, A. D. *Eur. J. Org. Chem.* **1999**, 451 and references cited.

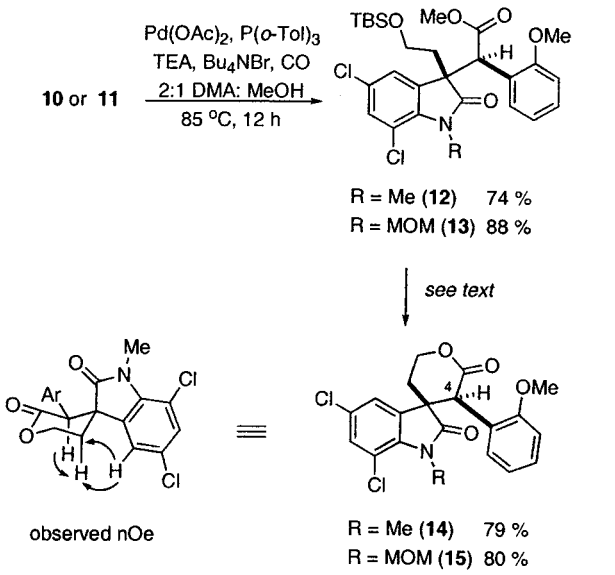
(10) This particular substituent was chosen based upon the putative structure for nomofungin, which had not been retracted at the start of this work.[3]

(11) (a) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1992**, *48*, 9373. (b) McCort, G.; Hoornaert, C.; Aletru, M.; Denys, C.; Duclos, O.; Cadilhac, C.; Guilpain, E.; Dellac, G.; Janiak, P.; Galzin, A.-M.; Delahaye, M.; Guilbert, F.; O'Connor, S. *Bioorg. Med. Chem.* **2001**, *9*, 2129.

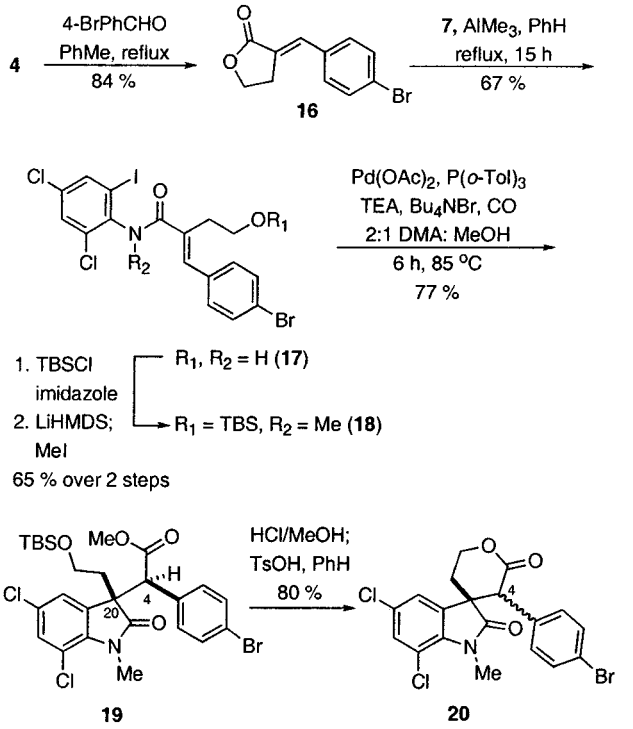
(12) The *E* geometry of benzylidene lactone **6** was established by nOe NMR experiments.

(13) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49.

Scheme 2



Scheme 3



The reactions were heated in a 2:1 mixture of DMA and MeOH under a balloon atmosphere of CO. Acrylamides **8** and **9** were first exposed to the Heck conditions, but no reaction occurred and only the starting amides were recovered unchanged. We believe this lack of reactivity is due to a low population of the rotamer needed for the initial Heck reaction to occur. On the other hand, the iodo *N*-methyl amide **10** readily cyclized under these conditions to yield the desired *N*-methyl lactam **12** in 74% yield (Scheme 2). Similarly, the iodo *N*-MOM amide **11** also underwent the desired Heck/carbonylation reaction to afford the *N*-MOM lactam **13** in slightly better yield. Both lactams **12** and **13** were isolated as single diastereoisomers having the stereochemistry shown (vide infra). This stereochemistry is the result of a net *syn* addition of the aryl palladium intermediate and CO across the *E* olefin. The *N*-methyl amide **12** was converted to the lactone **14** by using TBAF/NH_4F[14] to first remove the silyl protecting group followed by heating the alcohol ester with TsOH in benzene to give the lactone in 80% yield as a 3:1 β/α mixture of C4 epimers. nOe experiments established the conformation and configuration of the major epimer of lactone **14** to be as shown. Alternatively, using HCl in MeOH to remove the TBS group from *N*-MOM amide **13**, followed by heating with TsOH in benzene, afforded MOM lactone **15** in 79% yield as a single diastereoisomer. The conformation and configuration of **15** were proven by X-ray crystallography, where the lactone ring exists as a half-chair with the lactam carbonyl in a pseudo-axial position and the C4 methoxyarene in an equatorial position (see Supporting Information).

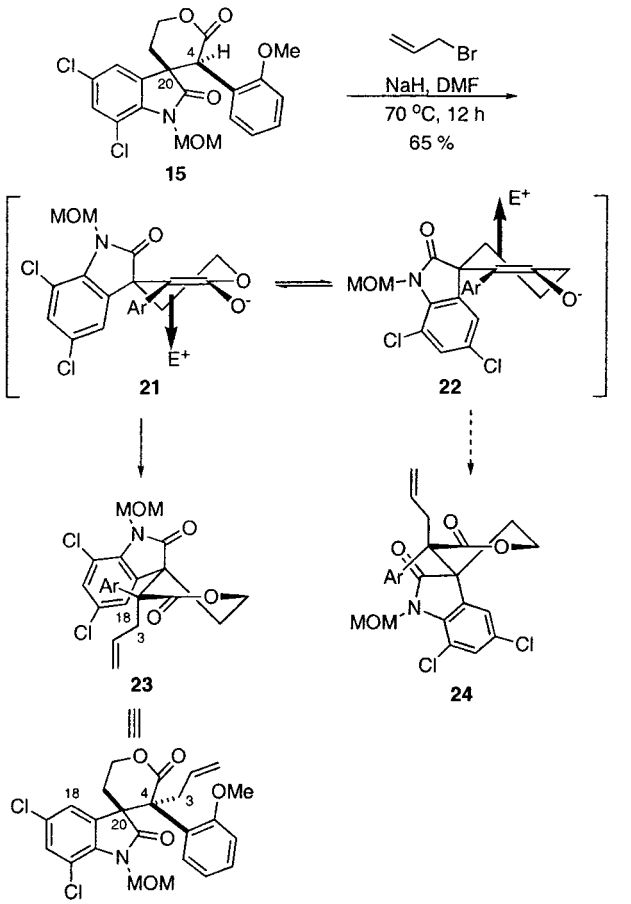
We have also explored the feasibility of having a potentially labile bromine present in the C ring of perophoramidine (**1**) during the cyclization. To that end, we prepared *E*-4-bromobenzylidene lactone **16** by a Wittig olefination of the ylide **4** with 4-bromobenzaldehyde in 84% yield (Scheme 3). Ring opening of the lactone **16** with iodo aniline **7** in the presence of trimethyl aluminum afforded acrylamide **17** in 67% yield. Conversion of the primary alcohol functionality of acrylamide **17** to its TBS ether and *N*-alkylation with MeI yielded the iodo *N*-methyl amide **18** in 65% overall yield. We were pleased to find that exposure of the bromo iodo amide **18** to our optimized tandem Heck conditions resulted in clean formation of the desired bromo dichlorolactam **19** in 77% yield as a single stereoisomer. As was done for Heck product **15**, bromo dichlorolactam **19** was cyclized to the bromo lactone **20** in 80% yield as an inseparable 5:1 β/α mixture of C4 epimers.

At this stage, the installation of the quaternary center at C4 of perophoramidine (**1**) was explored. Alkylation of the lactone **15** with various amide bases and allyl bromide at room temperature in THF proved sluggish. However, using NaH in DMF at 70 °C overnight resulted in the allylated lactone **23** in 65% yield as a single diastereomer along with a trace of starting material. Decoupling and nOe NMR experiments (H_3 vs H_{18} enhancement) showed that the allylation product had the correct stereochemistry for perophoramidine (**1**).

At this point we can only speculate as to the reasons for this stereochemical outcome. Allylation of the two half-chair forms of the enolates **21** and **22** might occur via axial attack by the electrophile to afford the observed product **23** and the C4 epimer **24**, respectively. One possibility is that the direction of attack in this slow allylation process reflects product stability.[15] In fact, calculations show **23** to be >2

(14) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.

Scheme 4



kcal/mol more stable than **24**.[16,17] In addition, allylation product **23** may gain additional stabilization via a Bürgi−Dunitz interaction[18] between a lactam oxygen lone pair and the π^* orbital of the lactone carbonyl group, which is not possible in isomer **24**. This type of interaction seems reasonable based on the X-ray structure of lactone **15**, where the distance between the oxygen lone pair and the lactone carbonyl carbon is about 2.8 Å, and the corresponding angle is approximately 110°.

In conclusion, we have developed an efficient approach to the synthesis of perophoramidine (**1**) via a halogen-selective tandem Heck/carbonylation sequence. We have demonstrated that the presence of the chlorines and bromine atoms and an *ortho* C ring substituent do not adversely affect the desired transformation. In addition, we have shown that the second quaternary center at C4 can be introduced in a stereoselective manner providing the requisite stereochemistry for the metabolite. Application of this strategy to a total synthesis of perophoramidine (**1**) is underway.

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Supporting Information Available: Experimental procedures for preparation of new compounds including spectral data, and X-ray data for compound **15** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034314D

(15) Evans, D. A. Stereoselective Alkylation Reactions of Chiral Metal Enolates. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, p 28.

(16) Molecular modeling calculations were performed with Serena Software PC Model 7.5.

(17) The boat conformers resulting from "equatorial" allylation of the enolates **21** and **22** were considerably higher in energy.

(18) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563. See also: (d) Nishide, K.; Hagimoto, Y.; Hasegawa, H.; Shiro, M.; Node, M. *Chem. Commun.* **2001**, 2394.