Natural Product Synthesis

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Synthesis of Oximidine II by a Copper-Mediated Reductive Ene–Yne Macrocyclization**

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Oximidine II (**1**, Figure 1) was isolated in 1999 by Hayakawa and co-workers and displays cytotoxicity at the ng mL^{-1} level in mutant rat fibroblasts.[1] Oximidine II belongs to the benzolactone enamide family of natural products,[2] which exert their biological activity through selective inhibition of mammalian vacuolar-type H^+-ATPases (V-ATPases).[3] Intrigued by its promise as an anticancer agent, our group sought a feasible synthetic route towards oximidine II.

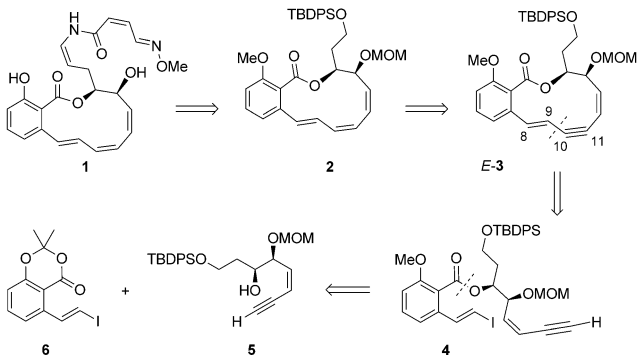
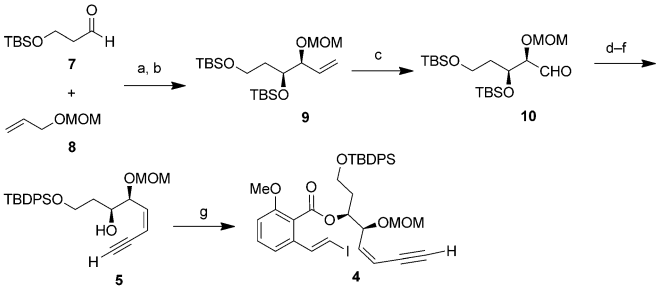


Figure 1. Retrosynthesis for oximidine II (**1**). TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, MOM = methoxymethyl.

The major challenge in the synthesis of oximidine II is the formation of its strained 12-membered macrolactone core, which contains nine contiguous sp^2-hybridized carbon atoms. The two previous total syntheses of oximidine II by the Porco[4a] and Molander[4b] groups demonstrated this difficulty. Joining C9 and C10 of the macrocyclic core of **1** through either ring-closing metathesis (Porco) or a Suzuki–Miyaura coupling (Molander) proceeded with yields of 48% and 42%, respectively. Other groups have reported similar challenges in forming this strained macrocycle in model systems.[5] Our retrosynthesis in Figure 1 utilizes an intramolecular Castro–Stephens reaction,[4,5b] in which intermediate **4** is employed to form the C9–C10 bond; a chemo- and stereoselective reduction of the alkyne unit in the cyclization product **3** generates the triene macrocyclic core **2**. The cyclization precursor **4** would be derived from the chiral aliphatic fragment **5** and aryl acetonide **6**.

The synthesis of precursor **4** (Scheme 1) began with an asymmetric Brown allylation[4,7] of aldehyde **7** with alkene **8**, followed by TBS protection of the newly formed secondary hydroxy group to furnish the enantioenriched product **9** in 81% yield as a single diastereoisomer (^{1}H NMR analysis) with 94:6 e.r. as determined by Mosher ester analysis.[8] Ozonolysis of intermediate **9** yielded aldehyde **10**, which was treated with the lithium anion of 1,3-bis(TIPS)-propyne[9] to afford the Peterson olefination product with a *Z*/*E* ratio of 10:1. Desilylation and reprotection of the alcohol as its monosilyl ether provided the aliphatic building block **5**. Reaction of aryl acetonide **6**[10] with the sodium alkoxide[4] of **5**, followed by quenching of the resultant phenolate with



Scheme 1. Synthesis of **4**: a) *s*BuLi, (+)-Ipc$_2$BOMe, BF_3·OEt_2, −78 to 0 °C, 81%, 94:6 e.r.; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, quantitative; c) O_3, CH_2Cl_2, −78 °C, then Me_2S; d) 1,3-bis(TIPS)-propyne, *n*BuLi, THF −78 °C; e) TBAF, THF; 51% over three steps; f) TBDPSCl, imidazole, DMAP, DMF, 80%; g) NaHMDS, THF, 0 °C, then **5**, then Me_2SO_4, 89%; Ipc = isopinocampheyl, OTf = trifluoromethanesulfonate, TIPS = triisopropylsilyl, THF = tetrahydrofuran, TBAF = tetra-*n*-butylammonium fluoride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazane.

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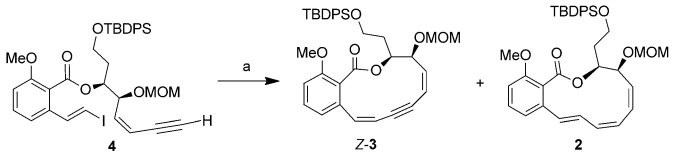
Me_2SO_4 produced **4**, the key intermediate for the macrocyclization step.

Similar to our previously reported results[4] reaction of compound **4** under catalytic Castro–Stephens conditions[6] (Scheme 2) afforded the energetically more stable macrocycle



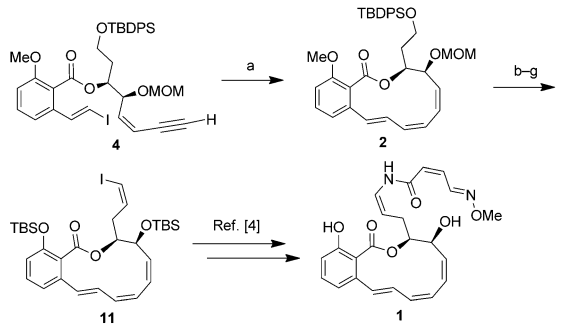
Scheme 2. Castro–Stephens macrocyclization of **4**: a) CuI, PPh_3, K_2CO_3, DMF, 120 °C, 18 % (*Z*-**3**) and 8 % (**2**).

Z-**3** in 18 % yield and none of the kinetic product *E*-**3**. Careful analysis of the reaction mixture surprisingly, revealed the presence of a small amount (8 %) of the partially reduced triene macrocycle **2**, featuring the required oximidine triene system.

Given these findings, we concluded that the alkyne-containing macrocycle *E*-**3** was highly reactive and could undergo subsequent transformations such as C8–C9 isomerization to form the thermodynamically more stable *Z*-**3** product, or reduction of the alkyne to furnish **2**. We then hypothesized that it might be possible to find reaction conditions to optimize the conversion of reactive intermediate *E*-**3** to generate triene **2**. Our initial attempts involved addition of excess Cu^0 or CuI—potential reductant sources—to the reaction mixture. However, these reactions resulted only in the isolation of dienyne *Z*-**3** and triene **2** in similar ratios. We then hypothesized that a copper hydride species could be responsible for the in situ reduction of the alkyne in *E*-**3**.

Indeed, exposing **4** to the reaction conditions reported by Stryker et al. for the generation of $[CuH(PPh_3)]_6$[12] led to the isolation of only the reduced triene product **2** in 31 % yield. Dienynes *Z*-**3** or *E*-**3** were not detected in the reaction mixture. The optimal source of hydride for this one-flask macrocyclization/reduction transformation proved to be sodium formate, which exclusively generated the triene macrocycle **2** in a yield of 67 % (Scheme 3). This reductive cyclization was also mediated by $Cu(OAc)_2{\cdot}H_2O$, albeit furnishing lower yields (55 %) of the desired triene **2** but producing cleaner reactions. In order to exclude the possibility that reduction of *Z*-**3** had generated **2**, we subjected macrocycle *Z*-**3** to the optimized reductive cyclization conditions but isolated only starting material from the reaction mixture.

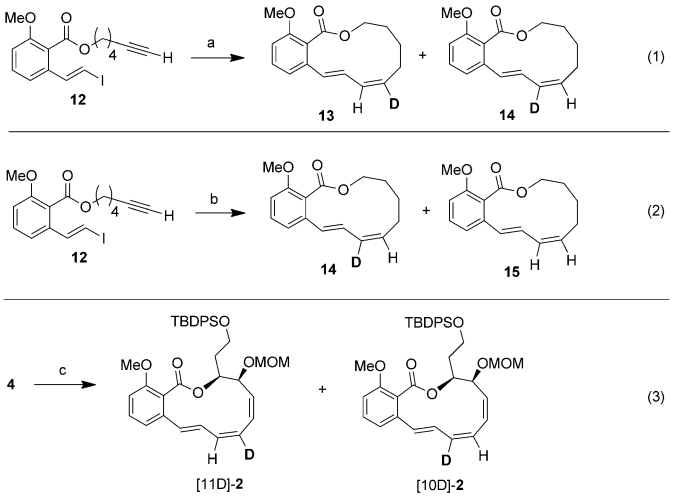
With a viable route to the triene core in hand, we completed the total synthesis of oximidine II (**1**; Scheme 3). Desilylation of triene **2**, oxidation to the corresponding aldehyde, and *Z*-selective iodo-olefination under Stork–Zhao conditions[13] generated the corresponding *Z*-vinyl iodide as the sole isomer (^{1}H NMR analysis) required for the penultimate amide coupling. Completion of the formal synthesis of oximidine II was achieved after removal of the alkyl ether protecting group



Scheme 3. Synthesis of oximidine II (**1**): a) CuI, PPh_3, K_2CO_3, HCO_2Na, DMF, 120 °C, 67 %; b) TBAF, THF, 94 %; c) Dess–Martin periodinane, CH_2Cl_2, 86 %; d) IH_2CPPh_3I, NaHMDS, HMPA, DMF, THF, 0 °C to RT to −78 °C, 80 %; e) CBr_4, iPrOH, 75 °C, 96 %; f) BCl_3, CH_2Cl_2, −78 °C, 94 %; g) TBSOTf, pyridine, CH_2Cl_2, 0 °C to RT, 80 %. HMPA = hexamethylphosphoramide.

and protection of the resultant diol as its bis-TBS ether to form known vinyl iodide **11**. Following Porco's protocol, we completed the synthesis of oximidine II (**1**) from intermediate **11**.[4]

To investigate the mechanism of this novel transformation from **4** to **2**, we turned to deuterium-incorporation studies using the readily accessible model compound **12** (Scheme 4).[10] Reaction of **12** with DCO_2Na as the deuterium source under the established reaction conditions led to a 9:1 mixture of monodeuterated products **13** and **14** [Eq. (1) in Scheme 4]. Since we did not observe the bisdeuterated product in the reaction mixture, we hypothesized that a purported vinyl copper intermediate (i.e. **18** in Figure 2) was likely quenched by protons present in solution (i.e. from $Cu(OAc)_2{\cdot}H_2O$, the alkynyl proton, or adventitious water). This hypothesis is supported by the experiment performed with **12** in the presence of HCO_2Na and excess D_2O [Eq. (2)



Scheme 4. Mechanistic investigation of reductive macrocyclization: a) $Cu(OAc)_2{\cdot}H_2O$, PPh_3, K_2CO_3, DCO_2Na, DMF, 120 °C, 9:1 (**13**/**14**), 31 %; b) $Cu(OAc)_2{\cdot}H_2O$, PPh_3, K_2CO_3, HCO_2Na, D_2O, DMF, 120 °C, 1:8 (**14**/**15**), 34 %; $Cu(OAc)_2{\cdot}H_2O$, PPh_3, K_2CO_3, DCO_2Na, DMF, 120 °C, 5:3 ([11D]-**2**/[10D]-**2**), 65 %.

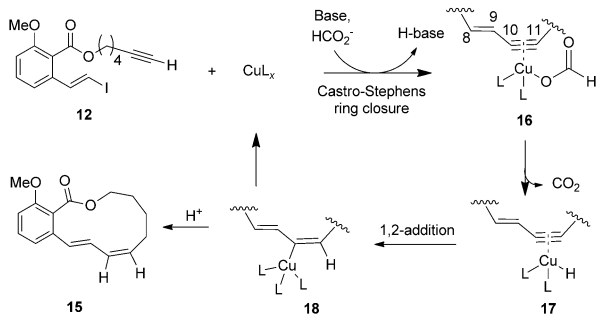


Figure 2. Mechanistic proposal for the reductive macrocyclization.

in Scheme 4], which generated monodeuterated product **14** and nondeuterated product **15** in a 1:8 ratio by ^{1}H NMR analysis. We also subjected intermediate **4** to the optimized reductive cyclization conditions in the presence of DCO_2Na [Eq. (3) in Scheme 4] and observed the C11- and C10-deuterated products [11D]-**2** and [10D]-**2** in a 5:3 ratio by ^{1}H NMR analysis.[10] Since it is possible that protons could be generated from the decomposition of DMF,[14] we carried out the reaction in [D_7]DMF as the solvent, but could not detect any deuterium incorporation.

Based on the deuterium-labeling studies, we propose the mechanism of this reductive macrocyclization to occur as shown in Figure 2. The stereoselective ring closure of **12** by means of a Castro–Stephens reaction[15] forms the alkyne-containing 8*E* macrocycle **16**, with the copper atom remaining coordinated to the alkyne, thereby stabilizing the C8–C9 *E*-olefin geometry and preventing double-bond isomerization. Expulsion of CO_2 from formate forms the requisite Cu–H species **17**, which then undergoes a 1,2-addition across the triple bond to afford the vinyl copper intermediate **17** in which the copper is preferentially bound to C10. As shown in Scheme 4 [Eqs. (2) and (3)], a C11–Cu intermediate must form as well since C11-deuterated products were formed also. The ratio of C10 versus C11 deuteration is presumably influenced by the electronic properties of the alkyne since model compound **12** and cyclization precursor **4** gave different ratios of deuterium incorporation. Finally, protonation of the copper metal species yields the reduced macrocycle **15**. The interception of reactive intermediate **16** with the hydride species is presumably key to the success of the reaction, because subjecting alkynyl macrocycle *Z*-**3** to the same reaction conditions led only to the recovery of starting material.

In summary, the synthesis of oximidine II was completed in a total of 14 steps and in 9.2% overall yield. An unprecedented Cu-mediated reductive Castro–Stephens macrocyclization was the key step to form the triene macrocycle in 67% yield. This methodology should prove useful in the construction of other macrocycles. Studies are underway to explore the scope of this chemistry.

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