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Synthesis of Oximidine II Via a Cu-Mediated Reductive Ene-Yne Macrocyclization**

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Abstract

An intramolecular copper-mediated reductive Castro-Stephens reaction furnished a key macrocyclic triene intermediate for the total synthesis of oximidine II. Herein we describe the total synthesis of the natural product as well as studies to deduce the mechanism of this unprecedented reaction.

Keywords

natural product; anti-cancer; macrocyclization; copper-mediated reactions; total synthesis

Oximidine II (**1**, Figure 1) was isolated in 1999 by Hayakawa and coworkers, displaying cytotoxicity at the ng/mL level in mutant rat fibroblasts.^[1] Oximidine II belongs to the benzolactone enamide family of natural products,^[2] which exert their biological activity

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through selective inhibition of mammalian vacuolar-type H⁺-ATPases (V-ATPases).^[3] Intrigued by its promise as an anti-cancer agent, our group sought a feasible synthetic route towards oximidine II.

The major challenge in the synthesis of oximidine II is the formation of its strained 12-membered macrolactone core that contains nine contiguous sp²-hybridized carbon atoms. The two previous total syntheses of oximidine II by the Porco^[4] and Molander^[4] groups demonstrated this difficulty. Joining C9 and C10 of the macrocyclic core of **1** through either a RCM approach (Porco) or a Suzuki-Miyaura coupling (Molander) provided yields of 48% and 42%, respectively. Other groups have reported similar challenges in forming this strained macrocycle in model systems.^[5] Our retrosynthesis is shown in Figure 1, which utilizes an intramolecular Castro-Stephens reaction^[4,5b], employing intermediate **4**, to form the C9–C10 bond, followed by a chemo- and stereoselective alkyne reduction of cyclization product **3** to generate the triene macrocyclic core **2**. The cyclization precursor **4** would be derived from chiral aliphatic fragment **5** and aryl acetonide **6**.

The synthesis of precursor **4** is shown in Scheme 1 and began with an asymmetric Brown allylation^[4,7] of aldehyde **7** with alkene **8**, followed by TBS protection of the newly formed secondary hydroxyl group to furnish the enantioenriched product **9** in 81% yield as a single diastereoisomer (¹H NMR) in a 94:6 e.r. as determined by Mosher ester analysis.^[8]

Ozonolysis of intermediate **9** yielded aldehyde **10**, which was reacted with the lithium anion of 1,3-bis(TIPS)-propyne^[9] to afford the Peterson olefination product in a 10:1 *Z:E* ratio. Desilylation and reprotection of the alcohol as its monosilyl ether provided 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 Me₂SO₄ 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 *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 Cu⁰ or CuI – potential reductant sources – into the reaction mixture. However, these reactions led only to the isolation of similar ratios of dienyne *Z*-**3** and triene **2**. 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 conditions reported by Stryker for the generation of [CuH(PPh₃)]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•H₂O, 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 as shown in 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 (¹H NMR) required for the penultimate amide coupling. Completion of the formal synthesis of oximidine II was achieved after removal of the alkyl ether protecting group 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 DCO₂Na as the deuterium source under the established reaction conditions led to a 9:1 mixture of *mono*-deuterated products **13** and **14** (eq 1, Scheme 4).

Since we did not observe the *bis*-deuterated 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•H₂O, the alkynyl proton, or adventitious water). This hypothesis is supported by the experiment performed with **12** in the presence of HCO₂Na and excess D₂O (eq. 2, Scheme 4), which generated a 1:8 ratio of mono-deuterated product **14** and non-deuterated product **15** by ¹H NMR analysis. We also subjected intermediate **4** to the optimized reductive cyclization conditions in the presence of DCO₂Na (eq. 3, Scheme 4) and observed a 5:3 ratio of C11 and C10 deuterated products **11D-2** and **10D-2** by ¹H 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** via 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, thereby preventing double bond isomerization. Expulsion of CO₂ 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 (equ 2 and 3), a C11–Cu intermediate must form as well since C11 deuterated products were formed also. The ratio of C10 vs. 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 14 total 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.

Supplementary Material

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Figure 1.

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

Figure 2.
Mechanistic proposal for the reductive macrocyclization.

Scheme 1.

Synthesis of **4**: a) *s*BuLi, (+)-Ipc₂BOMe, BF₃•OEt₂, -78 to 0 °C, 81%, 94:6 *e.r.*; b) TBSOTf, 2,6-lutidine, CH₂Cl₂, quantitative; c) O₃, CH₂Cl₂, -78 °C, then Me₂S; 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 Me₂SO₄, 89%; Ipc = isopinocampheyl, OTf = trifluoromethanesulfonate, TIPS = triisopropylsilyl, THF = tetrahydrofuran, TBAF = tetra-*n*-butylammonium fluoride, DMF = *N,N*-dimethylformamide, HMDS = hexamethyldisilazane.

Scheme 2.

Castro-Stevens macrocyclization of **4**: a) CuI, PPh₃, K₂CO₃, DMF, 120 °C, 18% (**Z-3**) and 8% (**2**).

Scheme 3.

Synthesis of oximidine II (1): a) CuI, PPh₃, K₂CO₃, HCO₂Na, DMF, 120 °C, 67%; b) TBAF, THF, 94%; c) Dess-Martin periodinane, CH₂Cl₂, 86%; d) IH₂CPPh₃I, NaHMDS, HMPA, DMF, THF, 0 °C to RT to -78 °C, 80%; e) CBr₄, iPrOH, 75 °C, 96%; f) BCl₃, CH₂Cl₂, -78 °C, 94%; g) TBSOTf, pyridine, CH₂Cl₂, 0 °C to RT, 80%. HMPA = hexamethylphosphoramide.

Scheme 4.

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