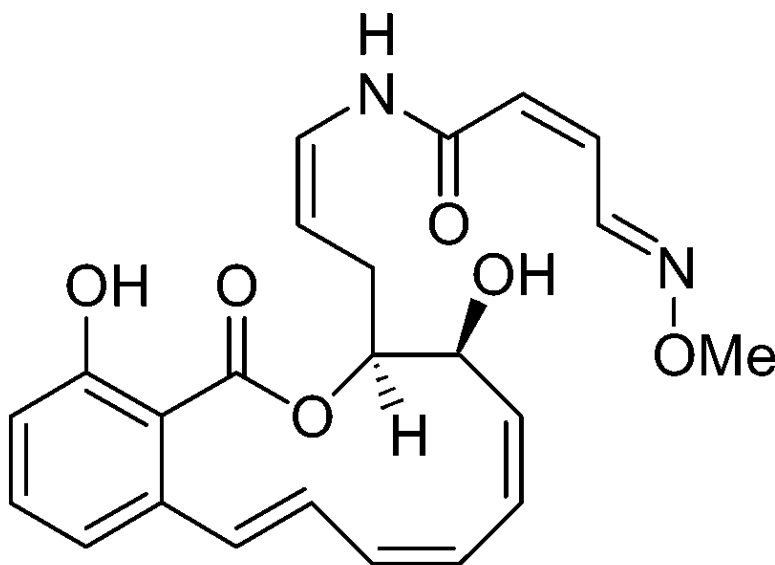


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Total Synthesis of the Salicylate Enamide Macrolide Oximidine II¹

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Oximidines I (**1**)¹ and II (**2**) (Figure 1) are closely related metabolites isolated from *Pseudomonas sp.* Q52002 which display potent antitumor activity. Relative and absolute stereochemistry assignments were based on extensive NMR studies, including modified Mosher ester analysis.² Recently, **1**, **2**, and other salicylate enamide macrolides such as the lobatamides³ and salicylhalamides⁴ have been shown to selectively inhibit mammalian vacuolar-type proton ATPase.⁵ Both **1** and **2** contain a highly unsaturated 12-membered macrolactone and (*Z*)-enamide side chain, differing only in epoxidation at C12–C13. Oximidine II possesses an (*E,Z,Z*)-conjugated triene within the macrolactone, which is very uncommon in natural products.⁶ Recent reports have documented approaches to the enamide side chain⁷ and core structures⁸ of the oximidines. Herein, we report the first total synthesis of (-)-oximidine II (**2**), employing an uncommon ring-closing metathesis of a bis-diene to construct the macrocyclic triene core.⁹

Our retrosynthetic analysis of oximidine II is shown in Figure 2. We planned to utilize copper-mediated amidation¹⁰ of (*Z*)-vinyl iodide **3** and amide **4**^{10a} for the late-stage introduction of the (*Z*)-enamide side chain. To construct the macrocyclic triene core, we first considered ring-closing metathesis (RCM)¹¹ of bis-diene substrate **5**. We anticipated that the strained, macrocyclic triene would be prone to ring-opening metathesis and therefore hoped to form the ring using kinetic control¹² by alteration of the protective groups (P₁–P₃) and diene substitution pattern of **5**.

We initiated our studies to prepare terminal diene fragments **6** and **7**.¹³ The synthesis commenced with asymmetric allylboration¹⁴ of aldehyde **8**¹⁵ to afford **9** as a single diastereomer in 80% yield (90% ee) (Scheme 1). The secondary alcohol was silylated, and the terminal olefin was oxidized to aldehyde **10** by a two-step procedure. Using Yamamoto's protocol,¹⁶ we converted aldehyde **10** to the desired *cis*-diene **6** after desilylation. Treatment of **6** with NaHMDS, followed by addition of acetonide **7** (prepared by Stille coupling¹⁷ of triflate **11**^{10b} and dienyl stannane **12**¹⁸), afforded bis-diene **13**, which was silylated to provide compound **14**. Attempted MOM deprotection of **14** with BBr₃ unexpectedly afforded the 1,3-dioxepan **15**, which was desilylated to phenol **16**.

With substrates **13**–**16** in hand, we examined their reactivity in RCM reactions.¹⁹ Treatment of all substrates with Ru catalyst **17** afforded products resulting from reaction of the *trans*-diene and gave no observable further conversion.²⁰ When treated with catalyst **18**, substrates **13** and **14** reacted with the *trans*-diene and gave no further conversion (CH₂Cl₂, reflux, 3 h). These results suggested that the *trans*-diene of substrates **13** and **14** was the initiation site for RCM, but that macrocyclization was nonproductive. Constrained substrates **15** and **16** afforded oligomeric products (20 min). In addition, HPLC-MS analysis indicated trace formation of 10-membered ring product(s) for substrate **16**, but no desired macrocyclic triene.

On the basis of these results, we next incorporated a *trans*-methyl group on the more reactive *trans*-diene in an effort to initiate the RCM at the terminus of the *cis*-diene. Synthesis of second

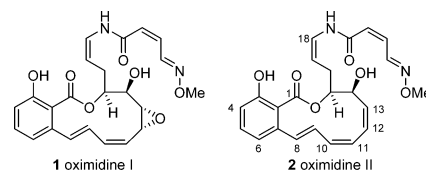


Figure 1. Structures of oximidines I (**1**) and II (**2**).

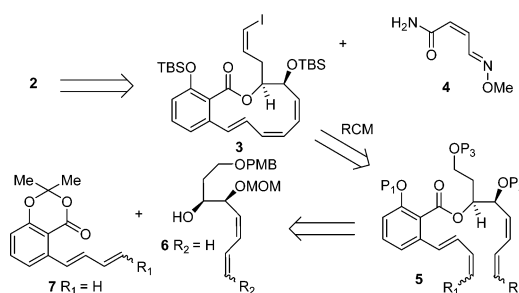
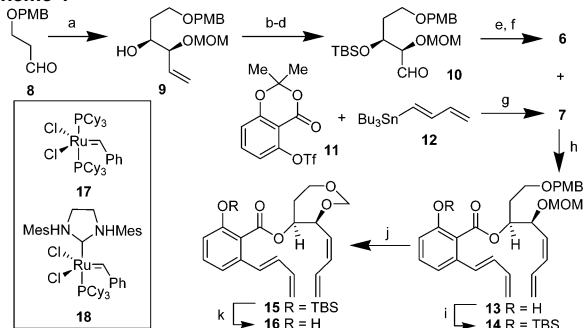


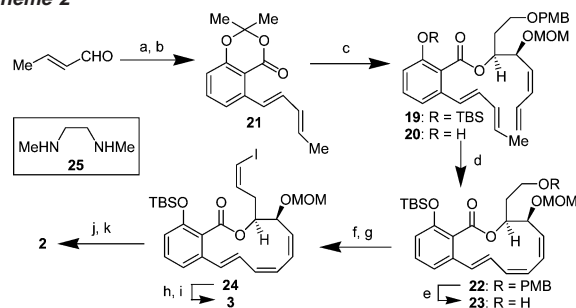
Figure 2. Retrosynthetic analysis of oximidine II.

Scheme 1^a



^a Conditions: (a) allyl methoxymethyl ether, ^tBuLi, (+)-Ipc₂BOME, BF₃·OEt₂, –78 to 0 °C, 80%; (b) TBSCl, imidazole, DMF, 94%; (c) cat. OsO₄, NMO, THF/H₂O; (d) K₂CO₃, Pb(OAc)₄, MeOH, 0 °C; (e) ^tBuLi, allyldiphenylphosphine, Ti(OⁱPr)₄, THF, –78 to 0 °C; then MeI; (f) TBAF, THF, 71% (four steps); (g) Pd₂dba₃, P(2-furyl)₃, LiCl, DMF, 60 °C, 89%; (h) **6**, NaHMDS, then **7**, THF, 0–25 °C, 95%; (i) TBSCl, imidazole, CH₂Cl₂, 95%; (j) BBr₃, CH₂Cl₂, –78 °C, 35%; (k) TBAF, THF, 0 °C, 60%.

generation substrate **19** (Scheme 2) was initiated by homologation²¹ of (*E*)-crotonaldehyde to afford a dienyl stannane which coupled with **11** to furnish the desired (*E,E*)-diene **21**. Treatment of **6** with NaHMDS, followed by addition of **21** and silylation, provided bis-diene **19** in a one-pot procedure. After considerable experimentation, we found that treatment of **19** with 5 mol % **18** in CH₂Cl₂ (2 mM, reflux, 70 min) afforded the oximidine II core **22** in 48% yield (one recycle) accompanied by oligomeric products. Extended reaction time resulted in decomposition of both starting material and product. It should be noted that under the same condition, phenol **20** did not undergo RCM but afforded only oligomeric products. Monte Carlo conformational searches on model compounds **A** and **B** (Figure 3) show a potential rationale for control of the C10–C11 olefin geometry by protection of the phenol.^{10b,13}

Scheme 2^a

^a Conditions: (a) CrCl₂, DMF, Bu₃SnCHBr₂, THF; (b) **11**, Pd₂dba₃, P(2-furyl)₃, LiCl, DMF, 80 °C, 61% (two steps); (c) **6**, NaHMDS, THF, 0–25 °C; then TBSCl, imidazole, 100%; (d) **18** (5 mol %), CH₂Cl₂, reflux, 48% (one recycle); (e) DDQ, CH₂Cl₂/H₂O (10/1), 0–25 °C, 93%; (f) PDC, 4 Å mol. sieves, CH₂Cl₂; (g) (Ph₃P⁺CH₂I)⁻, NaHMDS, THF, –78 to 25 °C, 60% (two steps); (h) CBr₄, ⁱPrOH, 75 °C, 83%; (i) TBSOTf, 2,6-lutidine, CH₂Cl₂, –78 to 0 °C, 93%; (j) **4**, CuTC, **25**, K₂CO₃, 50 °C; (k) HF–pyridine/pyridine, THF, 44% (two steps).

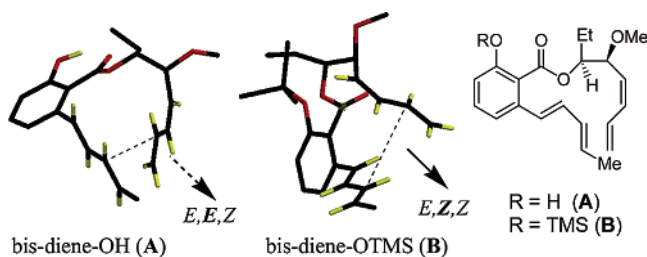


Figure 3. Representative reactive conformers of ring-closing metathesis substrates **A** and **B** (dashed lines indicate newly formed C10–C11 bonds).

For phenol substrate (**A**), the salicylate carbonyl maintains near planarity with the aromatic ring, leading to the predicted formation of a high energy and potentially reactive (*E,E,Z*)-triene.²² In contrast, silylation of the phenol forces the carbonyl out-of-plane from the benzene ring;²³ subsequent rotation of the C8–C9 bond affords the desired (*E,Z,Z*)-macrocyclic triene.

To advance **22** to a substrate for copper-mediated vinylic amidation, the PMB ether was removed (DDQ), and the resulting alcohol **23** was oxidized with PDC. Wittig olefination using the Stork/Zhao protocol²⁴ led to **24** as a single olefin isomer. The MOM protecting group was cleanly removed under mild, acidic conditions (CBr₄, ⁱPrOH),²⁵ and the resulting alcohol was reprotected to afford (*Z*)-vinyl iodide **3**.

Amidation of **3** with oxime amide **4** using conditions reported earlier for (*E*)-vinyl iodides^{10a} led to low yield due to competitive elimination under basic conditions. After a model study involving evaluation of various ligands and bases,²² we found that **3** coupled smoothly with **4**, employing stoichiometric amounts of CuTC²⁶-*N,N'*-dimethyl-ethylenediamine (**25**)²⁷ and K₂CO₃ as base (50 °C). Oximidine II (**2**) was obtained after desilylation (HF–pyridine/pyridine) with retention of olefin geometry. Synthetic **2** was confirmed to be identical to natural oximidine II by the ¹H and ¹³C NMR spectra, mass spectrum, [α]_D, HPLC, and TLC *R_f* values in three solvent systems.

In summary, the first enantioselective synthesis of the salicylate enamide macrolide oximidine II has been accomplished using the RCM of a well-defined bis-diene substrate to construct the unusual

macrocyclic triene core, and stereoselective copper-mediated amidation of a (*Z*)-vinyl iodide to construct the enamide side chain. Further synthetic studies on the oximidines and their biological evaluation will be reported in due course.

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Supporting Information Available: Experimental procedures, theoretical calculation results, and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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