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Divergent and Stereocontrolled Synthesis of the Enamide Side Chains of Oximidines I/II/III, Salicylihalamides A/B, Lobatamides A/D, and CJ-12,950

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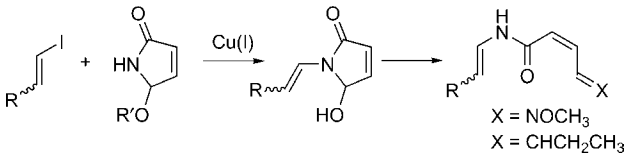
ABSTRACT



A unified strategy for the divergent and stereocontrolled introduction of the (*E*)- and (*Z*)-enamide side-chains of oximidines I, II, and III, salicylihalamides A and B, lobatamides A and D, and CJ-12,950 is detailed. The synthesis relied on the copper-promoted C–N coupling of (*E*)- and (*Z*)-vinyl iodides with a protected maleimide hemiaminal followed by deprotection and reaction of the resulting (*E*)- or (*Z*)-enelactam hemiaminals with *O*-methylhydroxylamine or propylidenetriphenylphosphorane.

The family of natural products known as the benzolactone enamides includes a diverse array of structures characterized by a benzo-fused macrolactone bearing an N-acylated enamine side-chain (Figure 1).[1] Members of this family include: (1) oximidines I, II, and III, isolated from *Pseudomonas* sp. that arrest the cell cycle in *ras* or *src*-transformed cells;[2] (2) salicylihalamides A and B, marine natural products isolated from the sponge *Haliclona* sp. that display a unique profile of differential cytotoxicity;[3] and, (3) the lobatamides, characterized by lobatamides A and D, isolated from *Aplidium* tunicates,[4,5] which exhibit activity similar to that of the salicylihalamides. These agents inhibit mammalian vacuolar ATPases, enzyme systems that are distributed widely in eukaryotic tissues and are involved in the regulation of pH gradients within intracellular compartments and secretory vesicles.[6] These agents have attracted considerable attention as important targets for total synthesis and as lead compounds for drug development.[1]

These antitumor agents share a common enamide side chain of variable stereochemistry at the enamine and α,β-unsaturated amide stereogenic double bonds. There have been a number of reports detailing synthetic routes to specific side chains,[7] but there is no general method for introduction of the oximidine, salicylihalamide, or lobatamide side-chains using a common synthetic strategy.

In this communication, we report a stereocontrolled method for the divergent synthesis[8] of model enamide side-

(1) For a review, see: Yet, L. *Chem. Rev.* **2003**, *103*, 4283.

(2) Oximidines I and II: Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153. Oximidine III: Hayakawa, Y.; Tomikawa, T.; Shin-ya, K.; Arao, N.; Nagai, K.; Suzuki, K.-i.; Furihata, K. *J. Antibiot.* **2003**, *56*, 905. For an approach to the triene lactone system of oximidine II, see: Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487. For the first total synthesis of oximidine II, see: Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040.

(3) Erickson, K. L., Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188.

(4) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805. Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., III; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968.

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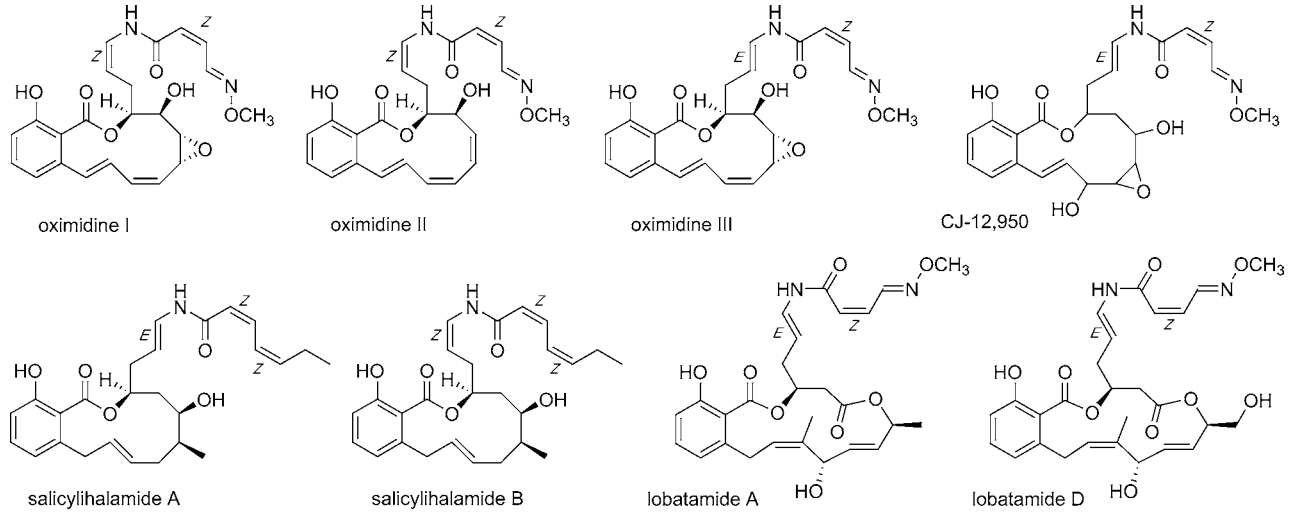
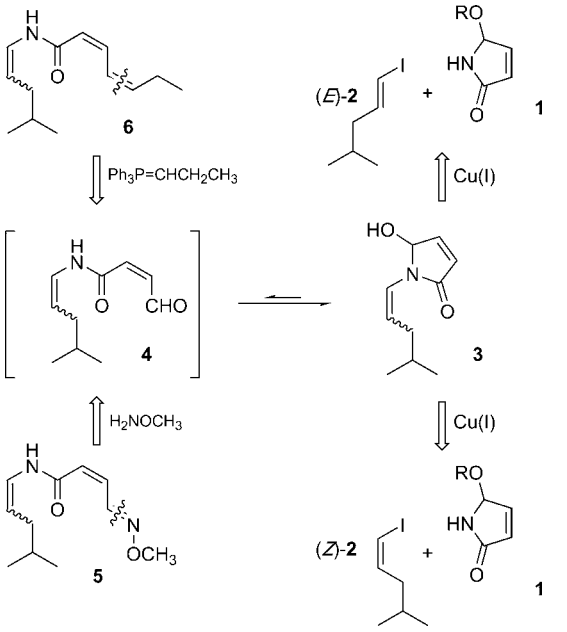


Figure 1. Structures of the benzolactone enamide antitumor agents.

chains (*E*)-**5**, characteristic of oximidine III, the lobatamides and CJ-12,950, (*Z*)-**5**, characteristic of oximidine I and II, (*E*)-**6**, present in salicylihalamide A, and (*Z*)-**6**, present in salicylihalamide B, all starting from isovaleraldehyde via the readily prepared vinyl iodides (*E*)-**2** and (*Z*)-**2** (Scheme 1). Our strategy uses cyclic hemiaminal **3**, presumably in equilibrium with acyclic aldehyde **4**: oxime formation provides **5**, whereas Wittig olefination provides **6**. The key intermediate **3** is synthesized by a stereospecific copper-promoted C−N bond formation[7f,9] between suitably protected precursor **1** and vinyl iodides (*E*)-**2** and (*Z*)-**2**. A central feature of this strategy is the recognition that the common cis stereochemistry found in the α,β-unsaturated amide alkene of side-chains of **5** and **6** could be introduced with total stereocontrol from within the cyclic framework of maleimide. Vinyl iodides (*E*)-**2** and (*Z*)-**2** can be prepared in a stereodivergent fashion from isovaleraldehyde by Takai[10] or Stork−Zhao[11] olefination, respectively.

Scheme 1



Reduction of maleimide[12] with $NaBH_4$ in the presence of $CeCl_3$ (MeOH, 0 °C, 1 h, 40% unoptimized) and protection of the resulting hemiaminal (*t*-BuMe_2SiCl imidazole, DMF, 25 °C, 12 h, 85%) afforded the central fragment **7** (Scheme 2). Copper-promoted coupling of **7** with vinyl iodides (*Z*)-**2**[13] or (*E*)-**2**[13a] effected C−N bond formation to provide (*Z*)-**8** (56%) and (*E*)-**8** (72%), respectively, in good yields that were comparable with those reported by other workers[7c] (Table 1). Cleavage of the silyl ether of (*Z*)-**8** and (*E*)-**8** occurred

(7) (a) Vinyl cuprate addition to an isocyanate: Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407. (b) Vinyllithium addition to an isocyanate: Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245. (c) Nonstereocontrolled elimination of bis-acylated aminal: Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645. (d) Acylation of a Teoc-protected enamine: Smith, A. B., III; Zheng, J. *Tetrahedron* **2002**, *58*, 6455. (e) From an acyl azide via a Curtius rearrangement and subsequent addition of a vinyllithium reagent: Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397. (f) Copper-promoted coupling of a vinyl iodide with a primary amide: Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333.

(8) For the origin of the concept of a divergent synthesis, i.e., the use of a common intermediate to prepare diverse members of a class of synthetic targets or family of natural products, see: Boger, D. L.; Mullican, M. L. *J. Org. Chem.* **1984**, *49*, 4045.

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Scheme 2

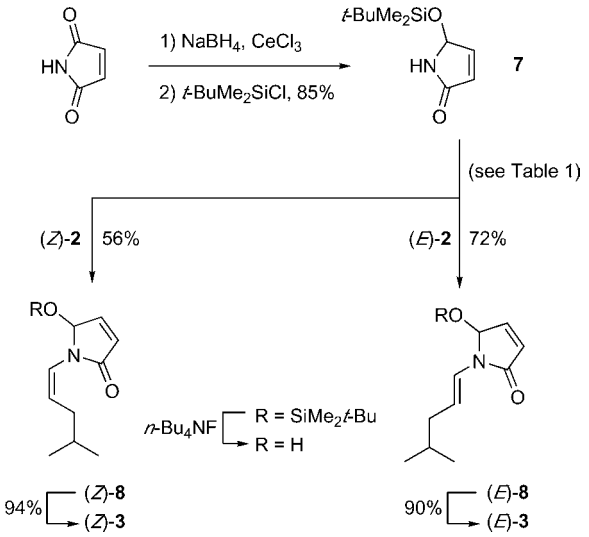
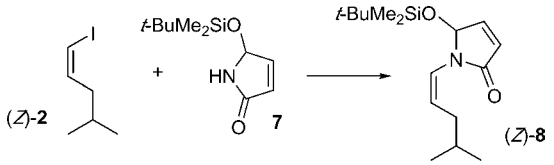


Table 1. Copper-Promoted C−N Bond Formation[a]



metal	ligand/base	solvent/temp/time	%
$Pd_2(dba)_3$	dppf/Cs_2CO_3	dioxane/100 °C/10 h	
$Pd_2(dba)_3$	xantphos/Cs_2CO_3	dioxane/100 °C/10 h	
$Pd_2(dba)_3$	xantphos/NaO*t*-Bu	toluene/100 °C/10 h	
$Pd(PPh_3)_4$	BINAP/Cs_2CO_3	dioxane/100 °C/10 h	
$Pd(PPh_3)_4$	dppf, NaO*t*-Bu	toluene/100 °C/10 h	
$Pd(OAc)_2$	dppf/Cs_2CO_3	dioxane/100 °C/10 h	
CuTC	Ph_3P or 1,10-phen	dioxane/90 °C/24 h	
CuTC	diamine/K_3PO_4	dioxane/90 °C/24 h	56
CuTC	DMED/K_3PO_4	dioxane/90 °C/24 h	42
CuI	diamine/K_3PO_4	dioxane/90 °C/24 h	46
CuTC	diamine/K_3PO_4	THF/70 °C/24 h	42
CuTC	diamine/K_3PO_4	toluene/90 °C/24 h	21
CuTC	diamine/K_3PO_4	NMP, DMF, or DMA	
CuTC	diamine/Rb_2CO_3	dioxane/90 °C/24 h	42
CuTC	diamine/K_2CO_3	dioxane/90 °C/24 h	33
CuTC + $Pd_2(dba)_3$	diamine/K_3PO_4	dioxane/90 °C/24 h	<5

[a] CuTC = copper(I) thiophenecarboxylate;[16] diamine = *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine; DMED = *N*,*N*′-dimethylethylenediamine; dppf = diphenylphosphinoferrocene; xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; dba = dibenzylidene acetone.

smoothly using *n*-Bu_4NF (THF, −20 °C, 10 min) to afford hemiaminals (*Z*)-**3** and (*E*)-**3**, respectively.

N-Arylation or N-vinylation of amides and lactams is often difficult, and there are surprisingly few reports of this reaction.[9b,c,f,14] There is a single report of the N-vinylation of the potassium salt of a lactam.[15] We found that the combination of Liebeskind's copper(I) thiophenecarboxylate (CuTc),[16] *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine,[17] K_3PO_4 as the base, and 1,4-dioxane as the solvent proved to be effective for the coupling of lactam **7** and *cis*-vinyl iodide (*Z*)-**2** (Table 1). An excess of amide **7** was necessary to effect complete consumption of the vinyl iodide, which is a favorably disposed ratio based on our intended use as the end game of a total synthesis. The (*Z*)- or (*E*)-configuration of the double bond of vinyl iodide was fully retained.

Screening of reaction conditions revealed copper(I), in the form of CuTc or recrystallized CuI,[18] to be the most effective metal catalysts, where improved yields were obtained by using CuTc. 1,2-Diamine ligands are excellent for promoting C−N bond formation in this system, but no coupling products were formed when triphenylphosphine or 1,10-phenanthroline was used as a ligand. Little difference was seen between K_3PO_4, Cs_2CO_3, or Rb_2CO_3 as bases, but K_2CO_3 was less effective and the reaction required a longer time to proceed to completion. Polar solvents such as DMF, DMA, NMP, or 1,2-cyclohexanediamine gave no desired coupling product; toluene was moderately effective, and 1,4-dioxane and THF proved to be the most generally useful solvents for the coupling.[19]

With optimized reaction conditions, the *trans*-vinyl iodide (*E*)-**2** provided higher yields in the C−N bond formation (72%) compared to the *cis*-vinyl iodide (*Z*)-**2** (56%). Palladium was completely unsuccessful as a catalyst for this C−N bond formation, and a variety of Pd catalysts and ligands were employed, including palladium sources such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and $Pd(OAc)_2$ and ligands such as dppf, BINAP, and xantphos, uniformly without success.[14,20]

Treatment of the hemiaminals (*Z*)-**3** and (*E*)-**3** with *O*-methylhydroxylamine hydrochloride led to the formation of the corresponding ring-opened *O*-methyloxime ether (*Z*)-**5** (78%), characteristic of oximidines I and II, (*E*)-**5** (71%), characteristic of oximidine III, lobatamides A and D, and CJ-12,950 (Scheme 3).

A hemiaminal is less reactive than the typically used hemiacetal or aldehyde, and to the best of our knowledge, this is the first report of the ring-opening reaction of a hemiaminal to form the corresponding oxime. The reaction of hemiaminal (*E*)-**3** bearing the *trans*-alkenyl group with *O*-methylhydroxylamine hydrochloride is sluggish compared to the corresponding hemiaminal (*Z*)-**3** bearing the *cis*-alkenyl

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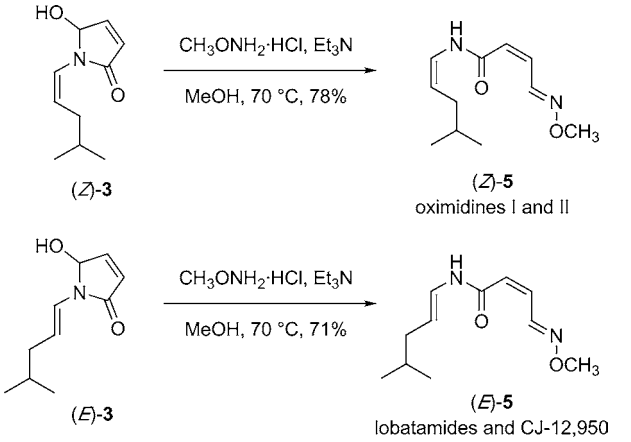
(17) Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta*. **1988**, *71*, 1999.

(18) Dieter, R. K.; Silks, L. A.; Fishpaugh, J. A.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679.

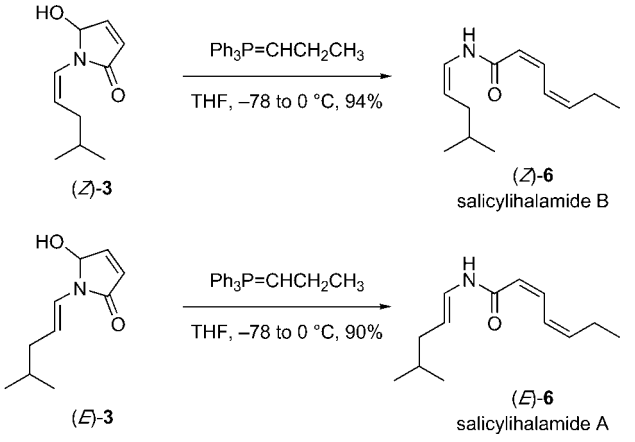
(19) In examples of amide coupling with a *trans*-vinyl iodide reported by Porco[7f] and Fürstner,[9d] the reaction was performed without ligands and polar aprotic solvents were used, contrasting our reaction conditions.

(20) (a) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun*. **2002**, 2362. (b) MacNeil, S. L.; Gray, M.; Briggs, L. E.; Li, J. J.; Snieckus, V. *Synlett* **1998,** 419. (c) Deboves, H. J. C.; Hunter, C.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 733. (d) Maes, B.; Jonckers, T.; Lemière, G.; Rombouts, G.; Pieters, L.; Haemers, A.; Dommisse, R. *Synlett* **2003**, 615. (e) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525.

Scheme 3



Scheme 4



group, and this reaction required an extended reaction time to reach completion. The success of this ring-opening is dependent upon the identity of the base used to neutralize the hydrochloride salt: with amine bases such as Et_3N, the desired oxime ethers (*Z*)-**5** or (*E*)-**5** were obtained in 78 and 71% yields, respectively. In the presence of stronger bases such as KOH, ring opening at the CO−N acyl bond and isomerization of the double bond of the resulting hydroxamate occurred. In the absence of base or in the presence of acetic acid, the reaction is not productive.

Cis-selective Wittig olefination of hemiacetals has been reported and proceeds effectively,[21] but to the best of our knowledge, there are no reports of the Wittig reaction of cyclic hemiaminals. The Wittig cis olefination of (*Z*)-**3** and (*E*)-**3** (Scheme 4) using propylidenetriphosphorane (generated from propyltriphenylphosphonium bromide by treatment with $KN(SiMe_3)_2$ in THF at −20 °C) proceeded uneventfully (THF, −78 to 0 °C, 30 min) and afforded (*Z*)-**6**, characteristic of salicylihalamide B, and (*E*)-**6**, characteristic of salicylihalamide A, in 94 and 90% yields, respectively.

(21) For representative examples, see: Busato, S.; Scheffold, R. *Helv. Chim. Acta.* **1994**, *77*, 92. Chauhan, K.; Aravind S.; Lee S.-G.; Falck, J. R.; Capdevila, J. H. *Tetrahedron Lett.* **1994**, *35*, 6791. Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1983**, *48*, 758.

Starting from isovaleraldehyde, installation of the enamide side-chains of the natural products oximidines I, II, and III, salicylihalamides A and B, lobatamides A and D, and CJ-12,950 was accomplished in an efficient, four-step reaction sequence. The synthetic sequence proceeds with two points of introduction of diversity. Stereodivergent installation of the corresponding *cis*- or *trans*-vinyl iodides by Takai or Stork−Zhao olefinations afforded (*Z*)-**2** and (*E*)-**2**, which were carried through a stereospecific copper-promoted C−N bond formation to afford (*Z*)-**8** and (*E*)-**8**. The second point of diversity introduction occurred at the stage of the cyclic hemiaminals (*Z*)-**3** and (*E*)-**3** via chemodivergent oxime formation or Wittig olefination. The methodology reported herein, while ingenuous in its formulation, proved to be effective when implemented. This work provides a unified synthetic strategy for enamide introduction for the total synthesis of the benzolactone family of antitumor agents.

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Supporting Information Available: Experimental procedures and spectral characterization of intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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