J|A|C|S
ARTICLES
Published on Web 07/30/2004

Formal Total Synthesis of Oximidine II via a Suzuki-Type Cross-Coupling Macrocyclization Employing Potassium Organotrifluoroborates

Gary A. Molander* and Florian Dehmel

Contribution from the Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

Received May 13, 2004; E-mail: gmolandr@sas.upenn.edu

Abstract: A formal total synthesis of oximidine II has been achieved, employing a Suzuki-type coupling approach to construct the highly strained, polyunsaturated 12-membered macrolactone. To achieve this goal, benefit was derived from the stability of potassium alkenyltrifluoroborates to establish conditions for the macrocyclization. The stereocontrolled formation of the *cis*-1,2-diol subunit was accomplished using a diastereoselective, reagent controlled addition to a chiral aldehyde utilizing the Carreira protocol. Advantage was taken of the Snieckus hydroborating reagent to gain access to the key trifluoroborate needed for the macrocyclization.

Introduction

During the past few years, many structurally related benzolactone enamides have been isolated from various natural sources. This family of compounds includes the oximidines, the lobatamides, the apicularenes, the salicylihalamides, and similar natural products (Figure 1).[1] Besides their common structural features, namely a 12- or 15-membered ring macrolactone and an α,β-unsaturated enamide side chain, they share a unique pharmacology. In biological testing, the salicylihalamides **5a/b** showed astonishing potency in the 60 cell line human tumor assay from the National Cancer Institute (NCI), with a mean panel GI_{50} of 7 nM. Even more exciting, these compounds revealed a novel mode of action unprecedented in the NCI's extensive database. Pharmacological studies showed that salicylihalamide A inhibits vacuolar-type (H^+)-ATPases (V-ATPases) with unparalleled selectivity. Consequently, V-ATPases may provide a novel molecular target for chemotherapeutic anticancer agents as well as for the amelioration of other serious afflictions (e.g., glaucoma, Alzheimer's disease and osteoporosis).[1i]

The oximidines, first isolated in 1999 from *Pseudomonas* sp. Q52002, show similarly promising biological activity.[1a] Oximidines I and II (**1b/a**) exhibit selective cytotoxicity at ng/mL levels for *ras* and *src* oncogene transformed cells. This biological inhibition was determined to affect the cell cycle at the G1 phase. As is the case with the salicylihalamides, V-ATPases appear to be the cellular target of these molecules.[2] Very recently, oximidine III (**1c**) was extracted from a *Pseudomonas sp.* QN05727 bacterial strain.[1b]

The tremendously exciting biology of the salicylihalamides **5a/b**, combined with their novel structural features and scarcity, has attracted the attention of several prominent synthetic organic and medicinal chemists. Most of these efforts have focused on

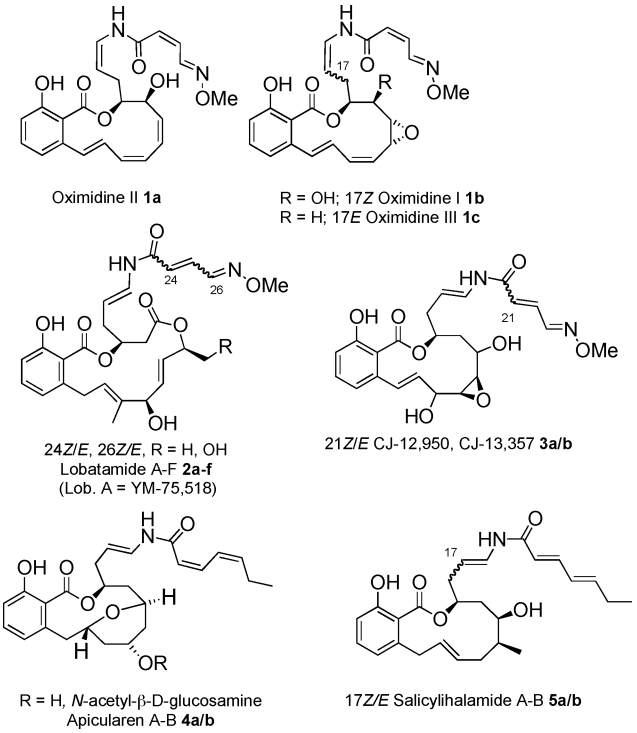


Figure 1. Oximidines and related natural products.

(1) (a) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153−155. (b) Hayakawa, Y.; Tomikawa, T.; Shin-Ya, K.; Arao, N.; Nagai, K.; Suzuki, H.-I.; Furihata, K. *J. Antibiot.* **2003**, *56*, 905−908. (c) Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968−8969. (d) 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*, 7805−7810. (e) Suzumura, K.-i.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiatmodjo, R. M.; Suzuki, K.-i.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573−76. (f) Dekker: K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14−20. (g) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913−919. (h) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075−1080. (i) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188−8192.

the ring closing metathesis reaction (RCM) as the key step to form the macrocyclic ring.[3] Besides the RCM approaches, macrocyclizations have been accomplished using intramolecular Suzuki[4a] or Stille couplings.[4b] For related members of this class, many total syntheses and synthetic approaches have also been reported.[5]

Porco and Wang recently published the first and thus far only total synthesis of oximidine II (**1a**).[6] Their elegant synthesis also leads to the macrolactone by a RCM approach and introduces the enamide side chain as the last stage employing Porco's efficient coupling method of vinyl halides and amides.[7] Although other macrolactonization routes and cross-coupling entries to the macrocyclic ring of the oximidines have been briefly explored,[8] difficulties in the construction of the highly strained 12-membered macrolactone have been encountered.[8a,b] The syntheses and synthetic approaches toward this entire class of natural products have been reviewed recently.[9]

Herein, we report a formal total synthesis of oximidine II that overcomes problems associated with other cross-coupling approaches to this molecule. The successful campaign employed an intramolecular Suzuki-coupling reaction of a highly functionalized potassium organotrifluoroborate for the macrocyclization.

Retrosynthesis

Our initial concept for the synthesis of the macrolactone is outlined in Figure 2. The key step envisioned was the macrocyclization via an intramolecular Suzuki-coupling reaction using potassium organotrifluoroborates.[10] Protecting group manipulations on the macrolactone would readily give alcohol **6**, which

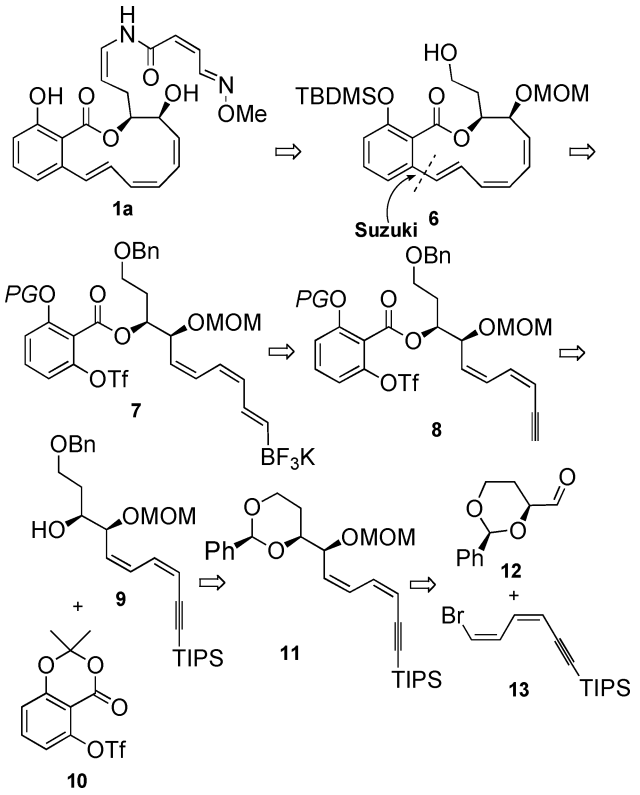


Figure 2. Retrosynthetic analysis of oximidine II **(1a)**.

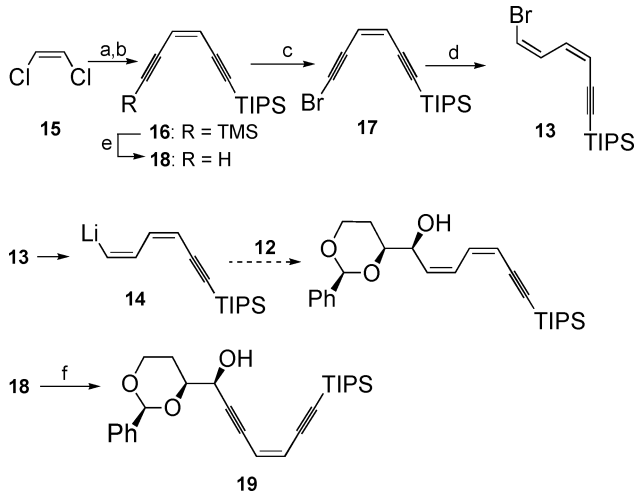
is an intermediate in Porco's oximidine II synthesis. Inherent in this strategy was the notion that Pd-catalyzed cross-coupling reactions have a distinct advantage over macrolactonizations in approaches to constrained systems.[8b] Thus, the postulated intermediate for the former reactions, a metallacycle, contains two additional long Pd−C bonds that would translate into reduced strain in the transformation leading to the polyolefinic system. Ring contraction by reductive elimination of the intermediate organometallic generates the desired macrolactone. In contrast to Sonogashira−Castro−Stephens type approaches,[8b] which create added strain owing to the introduction of the linear alkyne into the macrolactone, the Suzuki reaction precursor will already have in place all of the double bonds in the required geometry, which also represents the lowest energy configuration of the final product.[6,8a] The two stereogenic centers of the substrate would be created by a diastereoselective, chelation-controlled addition of organometallic nucleophiles derived from **13** to an α-chiral aldehyde, establishing the two stereogenic centers of the natural product.

Synthetic Efforts

The diene-yne nucleophile **14** was readily available in four steps employing a double Sonogashira coupling on *cis*-1,2-dichloroethylene **15** (Scheme 1).[11] The TMS-group in **16** was converted to the bromide, and a regioselective reduction of the brominated alkyne to the (*Z*,*Z*)-diene according to Brown[12] provided **13** in good overall yield. Bromine−lithium exchange

(2) (a) Boyd, M. R.; Farina, C.; Befiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114−120. (b) Beutler, J. A.; McKee, T. C. *Curr. Med. Chem.* **2003**, *10*, 787−796.
(3) (a) Yadav, J. S.; Srihari, P. *Tetrahedron: Asymmetry* **2004**, *15*, 81−89. (b) Herb, C.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 8129−813. (c) Yang, K. L.; Blackman, B.; Diederich, W.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Ahn, Y. M.; Georg, G. I. *J. Org. Chem.* **2003**, *68*, 10030−10039. (d) Yang, K. L.; Haack, T.; Blackman, B.; Diederich, W. E.; Srinivas Pusuluri, S. R.; Georg, G. I. *Org. Lett.* **2003**, *5*, 4007−4009. (e) Smith, A. B., III.; Zheng, J. Y. *Tetrahedron* **2002**, *58*, 6455−6471. (f) Wu, Y. S.; Liao, X. B.; Wang, R. F.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245−3253. (g) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286−5298. (h) Smith, A. B., III.; Zheng, J. Y. *Synlett* **2001**, 1019−1023. (i) Snider, B. B.; Song, F. B. *Org. Lett.* **2001**, *3*, 1817−1820. (j) Wu, Y. S.; Esser, L.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 4308−4310. (k) Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645−2648.
(4) (a) Bauer, M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 2205−2208. (b) Holloway, G. A.; Hügel, H. M.; Rizzacasa, M. A. *J. Org. Chem.* **2003**, *68*, 2200−2204.
(5) (a) Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357−3360. (b) Su, Q. B.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425−2430. (c) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104. (d) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549−5552. (e) Nicolaou, K. C.; Kim, D. W.; Baati, R. K.; O'Brate, A.; Giannakakou, P. *Chem. Eur. J.* **2003**, *9*, 6177−6191. (f) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701−3704. (g) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217−1220. (h) Shen, R. C.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889−7901. (i) Shen, R. C.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650−5651. (j) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289−1292. (k) Kühnert, S.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643−646.
(6) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040−6041.
(7) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333−1336.
(8) (a) Haack, T.; Kutkaya, S.; Snyder, J. P.; Georg, G. I. *Org. Lett.* **2003**, *5*, 5019−5022. (b) Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487−3490. (c) Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 7209−7212. (d) Scheufler, F.; Maier, M. E. *Synlett* **2001**, 1221−1224.
(9) Yet, L. *Chem. Rev.* **2003**, *103*, 4283−4306.
(10) (a) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107−109. (b) Molander, G. A.; Bernardi, C. *J. Org. Chem.* **2002**, *67*, 8424−8429. (c) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313−4327.
(11) (a) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410−7411. (b) Lu, Y.-F.; Harwig, C. W.; Fallis, A. G. *J. Org. Chem.* **1993**, *58*, 4202−4204. (c) Lu, Y.-F.; Harwig, C. W.; Fallis, A. G. *Can. J. Chem.* **1995**, *73*, 2253−2262.
(12) (a) Brown, H. C.; Blue, C. D.; Nelson, D. J.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6064−6067. (b) Hoshi, M.; Arase, A. *Synth. Commun.* **1997**, *27*, 567−572. (c) Zweifel, G.; Arzoumanian, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 5086−5088.

Scheme 1. Diastereoselective 1,2-Diol Formation[a]



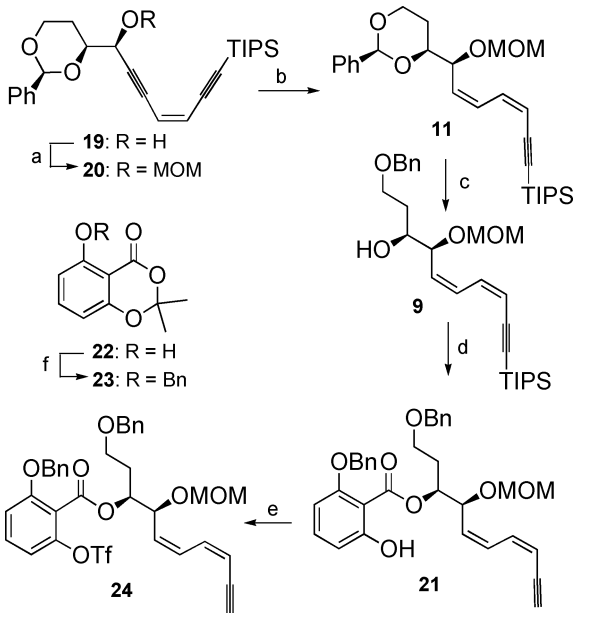
[a] Conditions: (a) triisopropylsilylacetylene, CuI, $Pd(PPh_3)_4$, NEt_3, Et_2O, rt, 93%; (b) trimethylsilylacetylene, CuI, $Pd(PPh_3)_4$, NEt_3, Et_2O, rt, 96%; (c) NBS, $AgNO_3$, acetone, rt, 99%; (d) *c*-Hex_2BH, pentane/THF, 0 °C, then AcOH, 45−60%; (e) K_2CO_3, MeOH/C_6H_6, 0 °C, 96%; (f) **12**, (+)-NME, $Zn(OTf)_2$, NEt_3, toluene, rt, 77%, dr >98:2. (+)-NME: *N*-Methylephedrine.

yielded the nucleophile **14**. However, addition of **14** to (2*R*,4*S*)-2-phenyl-[1,3]dioxane-4-carbaldehyde (**12**)[13] suffered from low yields (<20%) and low diastereoselectivities (dr < 2:1) under several reaction conditions.

The application of alkynyllithium or alkynylmagnesium compounds derived from **18** did not improve the diastereoselectivity of the carbonyl addition reaction to **12**. However, using the method developed by Carreira for the enantioselective addition of terminal alkynes to aldehydes,[14] the desired diastereoselective addition was achieved in good yield and excellent diastereoselectivity to afford **19**. An additional advantage of this reaction over the reaction employing the sensitive bromodiene **13** is the relative robustness of the alkyne precursor to standard laboratory conditions.

The addition product **19** was protected, and selective hydrogenation[15] of the sterically less hindered alkyne in the ene-diyne unit afforded the benzylidene acetal **11** (Scheme 2). Reductive cleavage of the benzylidene acetal was facilitated by coordination of DIBALH to the MOM protecting group of the substrate and provided selectively the secondary alcohol **9**.[16]

Scheme 2. Diene-yne Formation[a]



[a] Conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 86%; (b) H_2 (1 bar), Lindlar's cat. (70 w/w%), quinoline, hexanes, rt, 98%; (c) DIBALH, CH_2Cl_2, 0 °C, 69%; (d) i. NaHMDS, THF, 0 °C, then **23**, rt; ii. TBAF, THF, 0 °C, 58% (2 steps); (e) Tf_2O, pyr, 0 °C, 85%; (f) NaH, BnBr, DMF, 0 °C, 96%.

One of the most efficient methods to form esters of salicylates is the nucleophilic transesterification of the corresponding acetonides.[4b,5c−g,6,17] This transformation was incorporated into the current approach to oximidine II.

Thus, **9** was deprotonated and the resulting anion was reacted with benzyl protected **23** followed by desilylation to give **21**. Finally, the electrophilic moiety was introduced in the form of a triflate.

With **24** in hand, the substructure was established for a selective hydroboration of the terminal alkyne of the diene-yne subunit. Although precedented in related systems,[18] no efficient hydroboration conditions could be found to obtain any (*E*,*Z*,Z)-trienylboronic acid derivative that could be converted into the potassium organotrifluoroborate of **7** (Scheme 3). The investigated hydroboration reagents either lacked reactivity (catecholborane under various conditions;[18] pinacolborane and catalytic amounts of $Cp_2Zr(H)Cl$[19]), afforded extensive decomposition of the starting material ($HBBr_2$ and $HBCl_2$[20]) or exhibited difficulties during selective oxidation to the boronic acids (disiamylborane,[21] *c*-Hex_2BH[22] or *i*-PP_2BH[23]).

(13) (a) Isobe, M.; Ichikawa, Y.; Bai, D.-l.; Goto, T. *Tetrahedron Lett.* **1985**, *26*, 5203−5206. (b) Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *5*, 2896−2901. (c) Herradon, B. *Tetrahedron: Asymmetry* **1991**, *2*, 191−194. (d) Guo, Z.; Padmakumar, R.; Hollingsworth, R. I.; Radhakrishnan, K. V.; Nandakumar, M. V.; Fraser-Reid, B. *Synlett* **2003**, 7, 1067−1069. (e) Flögel, O.; Amombo, M. G. O.; Reissig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, H. *Chem. Eur. J.* **2003**, *9*, 1405−1415.

(14) (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605−2606. (b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020. (c) Boyall, D.; López, F.; Sasaki, H.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233−4236. (d) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807. (e) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373381. (f) Maezaki, N.; Kojima, N.; Tominaga, H.; Yanai, M.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1411−1414.

(15) (a) Schmidt, H. M.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1138−1142. (b) Corey, E. J.; Ritter, K.; Yus, M.; Najera, C. *Tetrahedron Lett.* **1987**, *28*, 3547−3550. (c) Gueugnot, S.; Alami, M.; Linstrumelle, G.; Mambu, L.; Petit, Y.; Larcheveque, M.; *Tetrahedron* **1996**, *52*, 6635−6646. (d) Hansen, T. V.; Stenstroem, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1407−1409. (e) Marquez, M. D. de; Thaller, V. *J. Chem. Res. Miniprint* **1985**, *4*, 1268. (f) Nicolaou, K. C.; Ladduwahetty, T.; Elisseou, E. M. *J. Chem. Soc. Chem. Commun.* **1985**, 1580−1581.

(16) For DIBALH deprotection on similar systems, see: (a) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033−3036. (b) Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu B. *Org. Lett.* **2000**, *2*, 1439−1442.

(17) See also: (a) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072−3080. (b) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217−1220.

(18) (a) de Lera, A. R.; Torrado, A.; Iglesias, B.; López, S. *Tetrahedron Lett.* **1992**, *33*, 6205−6208. (b) Torrado, A.; López, S.; Alvarez, R.; de Lera, A. R. *Synthesis* **1995**, 285−293. (c) Nicolaou, K. C.; Ramphal, J. Y.; Palazon, J. M.; Spanevello, R. A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 587−588.

(19) (a) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127−3128. (b) Batt, D. G.; Houghton, G. C.; Daneker, W. F.; Jadhav, P. K. *J. Org. Chem.* **2000**, *65*, 8100−8104.

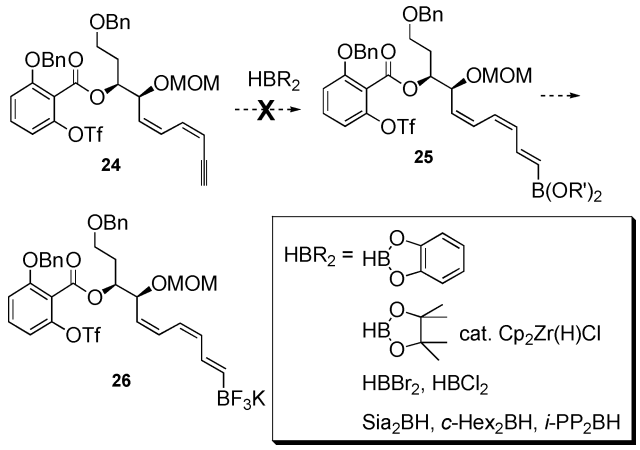
(20) (a) Soundararajan, R.; Matteson, D. S. *J. Org. Chem.* **1990**, *55*, 2274−2275. (b) Brown, H. C.; Basavaiah, D.; Bhat, N. G. *Organometallics* **1983**, *2*, 1309−1311.

(21) (a) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1984**, *25*, 761−764. (b) Miyaura, N.; Satoh, Y.; Hara, S.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2029−2031.

(22) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169−4172.

(23) *i*-PP_2BH= Di(isopropylprenyl)borane; Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399−3404.

Scheme 3. Attempted Hydroboration of 24



Revised Retrosynthesis

Because of the difficulties encountered with the selective hydroboration on the polyene-yne system, the proposed synthesis of oximidine II was revised (Figure 3). Another strategic disconnection for a Suzuki coupling approach lies between the (*E*)- and (*Z*)-configured olefin moieties in the ring (C9/C10), which would require the hydroboration of an arylated alkyne in the presence of a (*Z*,*Z*)-bromodiene. This precursor would again come from an esterification, this time between the secondary alcohol **29** and acetonide **30**. Although the salicylic acid precursor **30** could be derived in one step from **10**, the bromodiene unit in **29** would originate from an olefination of the enal **31**, which eventually would be obtained from the diastereoselective addition of propargyl acetate **32** to the chiral aldehyde **12**.[14a]

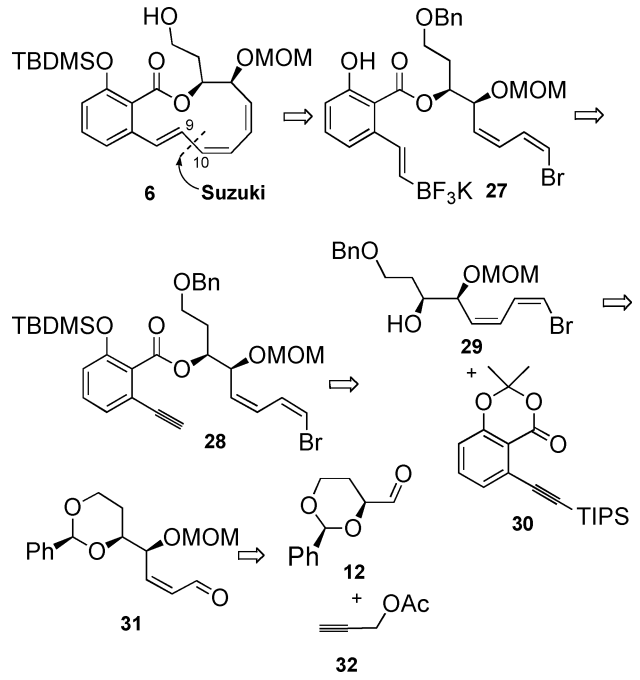
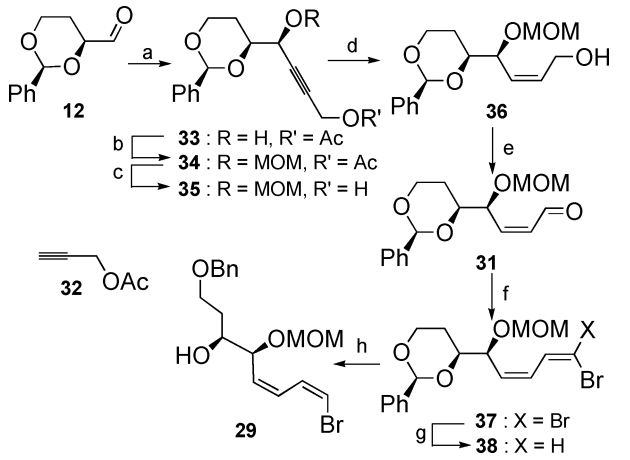


Figure 3. Revised retrosynthesis of **6**.

Formal Total Synthesis

The successful reaction sequence began with a diastereoselective addition to the enantiopure aldehyde **12** (Scheme 4). In this case, propargyl acetate **32** was used as the nucleophile in the Carreira protocol. The reaction took place with good yield and high diastereoselectivity. After protection of the alcohol, removal of the acetate, and partial reduction of the alkyne, allyl alcohol **36** was obtained in good overall yield. The installation of the (*Z*,*Z*)-bromodiene unit was achieved via a three-step protocol previously employed in similar systems.[24] The required secondary alcohol function was finally obtained by regioselective reductive cleavage of the benzylidene acetal.

Scheme 4. Formation of 29[a]



[a] Conditions: (a) **32**, (+)-NME, $Zn(OTf)_2$, NEt_3, toluene, rt, 89%, dr 91:9; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 86%; (c) K_2CO_3, MeOH, 0 °C; (d) H_2 (1 bar), Lindlar's cat. (70 w/w%), quinoline, hexanes, rt, 81% (3 steps); (e) IBX, DMSO, rt, 97%; (f) CBr_4, PPh_3, NEt_3, CH_2Cl_2, 0 °C, 84%; (g) *n*-Bu_3SnH, $Pd(PPh_3)_4$, C_6H_6, rt, 88%; (h) DIBALH, CH_2Cl_2, 0 °C, 75%. (+)-NME: *N*-Methylephedrine.

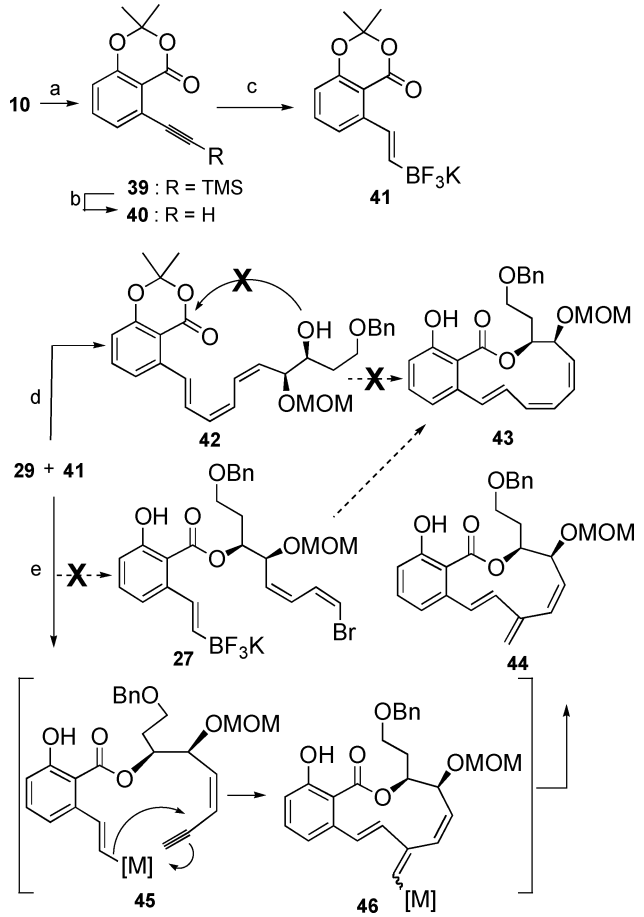
Having succeeded in synthesizing the diene **29**, our attention turned to the synthesis of the salicylate subunit. This requisite partner was easily derived from the protected triflate **10** in a Sonogashira type coupling with trimethylsilylacetylene (Scheme 5). After desilylation, the terminal alkyne was hydroborated using Snieckus' *i*-PP_2BH.[23] The resulting organoborane was converted directly into the corresponding potassium trifluoroborate **41**. Other boranes, such as catecholborane, were ineffective as hydroborating agents. This serves to highlight the utility of the Snieckus reagent as a precursor to trifluoroborates. This borane exhibits the reactivity and selectivity characteristics of most dialkylborane reagents, but has the added advantage of being easily transformed to boronic acids and their derivatives.

With subunits **29** and **41** in hand, both a macrolactonization strategy and the Suzuki cross-coupling approach to the macrolactone were accessible for comparison. An examination of the macrolactonization route was carried out first. This involved an initial intermolecular cross-coupling reaction between the two components. This was achieved under the conditions established for the reaction of vinyl halides and potassium vinyltrifluoroborates,[25] providing triene **42** in high yield. As expected, however, the macrolactonization using the esterification method (**42** to **43**) successfully employed in the intermolecular reaction (see Scheme 2) did not succeed. Presumably, this is due to the steric strain of the 12-membered ring as alluded to previously. Thus, it is likely that the constraints afforded by

(24) (a) Boger, D. L.; Ichikawa, S. Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161−4167. (b) Uemura, I.; Miyagawa, H.; Ueno, T. *Tetrahedron* **2002**, *58*, 2351−2358. (c) Uenishi, J.-i.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716−5717. (d) Uenishi, J.-i.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965−8975.

(25) Molander, G. A.; Felix, L., unpublished results.

Scheme 5. Formation of 41 and Coupling Reaction



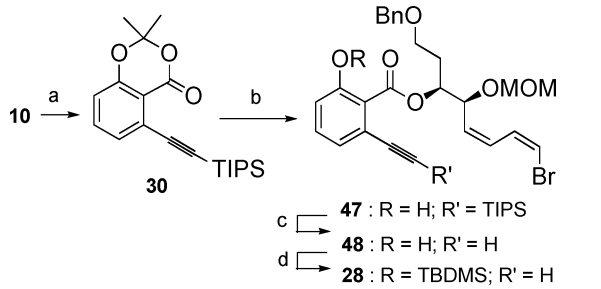
[a] Conditions: (a) trimethylsilylacetylene, CuI, $Pd(PPh_3)_4$, *i*-Pr_2NEt, THF, rt, 98%; (b) TBAF, THF, 0 °C, 99%; (c) 2,5-dimethylhexa-2,4-diene, BH_3·DMS, THF, 0 °C, then **31**, rt, then H_2O, then aq. CH_2O, ii. KHF_2, acetone, MeCN, H_2O, rt, 66%; (d) **29**, **41**, $Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O (10:1), reflux, 93%; (e) **29**, **41**, NaHMDS, DMF, 0 °C, then $Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O (10:1), reflux, 7%.

the conjugated triene prevented attack of the alkoxide on the lactone from the proper trajectory. Several attempts to activate the system toward macrolactonization were also unsuccessful.

Having exhausted nearly all other possibilities, our efforts finally focused on the Suzuki strategy utilizing trifluoroborate **27**. Surprisingly, intermolecular transesterification of **41** with the secondary alcohol **29** was unsuccessful under conditions previously established using THF as solvent (Scheme 5). The low solubility of the reacting partners was deemed to be problematic. Upon switching the solvent to DMF, a transesterification reaction of the acetonide was observed. The resulting product was directly subjected to the cross-coupling conditions. Interestingly, the only pure material isolated from the complex mixture proved to be the 11-membered macrolactone **44** bearing an exo-methylene moiety. The formation of this product can be attributed to the base lability of **29** in DMF, wherein the vinyl bromide is prone to dehydrohalogenation. The resulting enyne **45** appeared to have undergone an intramolecular carbometalation to form **46**, which, after protonation, led to the contracted macrolactone **44**.

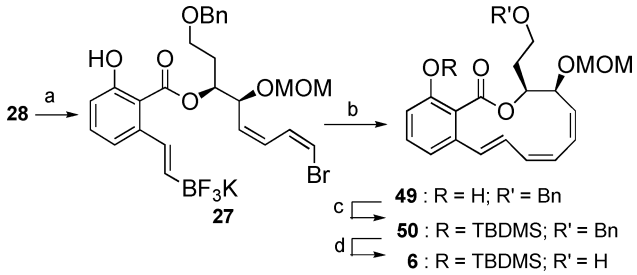
The final, successful campaign employed an intermolecular transesterification of lactone **30**, with formation of the trifluoroborate left to the penultimate step. To access the requisite

Scheme 6. Formation of 27[a]



[a] Conditions: (a) triisopropylsilylacetylene, CuI, $Pd(PPh_3)_4$, *i*-Pr_2NEt, THF, rt, 97%; (b) **29**, NaHMDS, THF, 0 °C; (c) TBAF, THF, 0 °C, 98% (2 steps); (d) TBDMSOTf, imidazole, DMAP, DMF, rt, 79%.

Scheme 7. Macrocyclization to 6[a]



[a] Conditions: (a) i. 2,5-dimethylhexa-2,4-diene, BH_3·DMS, THF, 0 °C, then **28**, rt, then H_2O, then aq. CH_2O, ii. KHF_2, acetone, MeCN, H_2O, rt, ~99%; (b) $Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O (10:1), 1 mM, reflux, 42% (2 steps); (c) TBDMSCl, imidazole, DMF, rt, 84%, (d) DDQ, CH_2Cl_2/pH=7-buffer (10:1), rt to reflux, 86%.

trifluoroborate, the secondary alcohol **29** was reacted with the protected alkyne **30** under the established conditions (THF solvent), providing **47** in high yields (Scheme 6). The more robust TIPS protection of the acetylene in **30** instead of the TMS-protected **39** proved to be beneficial under the nucleophilic reaction conditions. The TIPS group was removed and the phenol **47** was protected to afford the precursor for the hydroboration.

Again, application of the Snieckus reagent, *i*-PP_2BH, allowed selective hydroboration of the terminal alkyne, and the potassium trifluoroborate **27** was isolated in virtually quantitative yield as a slightly impure wax that was stable for weeks at ambient temperature in the air (Scheme 7). The ability to isolate and store a stable boron reagent allowed several reaction conditions to be tested for comparison in the crucial cyclization.

We were pleased to find that the cross coupling under previously developed reaction conditions gave the desired cyclized product **49** in 42% overall yield from alkyne **28** (Scheme 7). It is noteworthy that the reaction outcome depends on concentration, the palladium-catalyst precursor, and solvent (Table 1).

To complete the formal total synthesis, phenol **49** was then reprotected and the benzyl protecting group was removed with DDQ[26] to give **6**, which had been carried on by Porco to oximidine II. The synthesized product **6** showed identical NMR spectra to that quoted in the literature and a nearly identical optical rotation ($[\alpha]^{20}_{589}$ −153.2; literature −151.8[6]).

(26) For DDQ-deprotection of benzyl groups on olefinic substrates, see: (a) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009−3011. (b) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3197−3201.

Table 1. Macrocyclization Conditions[a]

entry	reaction conditions[a]	yield[b] (%)
1	$Pd(PPh_3)_4$ (10 mol %), Cs_2CO_3 (5 equiv), THF/H_2O (10:1), 5mM	16
2	$Pd(PPh_3)_4$ (10 mol %), Cs_2CO_3 (5 equiv), THF/H2O (10:1), 2mM	29[c]
3	$Pd(PPh_3)_4$ (10 mol %), Cs_2CO_3 (5 equiv), THF/H_2O (10:1), 1mM	42[c]
4	$Pd(PPh_3)_4$ (10 mol %), Cs_2CO_3 (5 equiv), DMF/H_2O (10:1), 2mM	8[c]
5	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10 mol %), Cs_2CO_3 (5 equiv), THF/H_2O (10:1), 2mM	18[c]

[a] The reaction mixture was heated at reflux for 20 h. [b] Isolated yield of **49**. [c] Yield over 2 steps from **28**.

Conclusion

We have completed a formal total synthesis of oximidine II employing a novel approach to construct the highly strained, polyunsaturated 12-membered macrolactone. To achieve this goal, benefit was derived from the stability of potassium alkenyltrifluoroborates to establish conditions for the macrocyclization via a Suzuki-type cross-coupling reaction. This has a demonstrated advantage over a macrolactonization approach to the molecule and other cross-coupling strategies as well. The stereocontrolled formation of the subunit possessing the two stereocenters was accomplished using the Carreira protocol in a diastereoselective, reagent controlled addition to a chiral aldehyde. Advantage was taken of the Snieckus hydroborating reagent to gain access to the key trifluoroborate needed for the macrocyclization. Finally, potassium organotrifluoroborates were applied for the first time to natural product synthesis, underscoring their promising characteristics in complex molecule synthesis.

Acknowledgment. We thank Professor John Porco and Xiang Wang for graciously providing us with copies of the ^1H and ^{13}C NMR spectra of **6**. We gratefully acknowledge the National Institutes of Health (GM 35249), Johnson & Johnson, and Amgen for generous support of this work. F.D. thanks the Deutsche Forschungsgemeinschaft for a postdoctoral stipend. We also thank Dr. R. Kohli for performing HRMS.

Supporting Information Available: Detailed experimental procedures including characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

JA047190O