

Development of a General, Sequential, Ring-Closing Metathesis/Intramolecular Cross-Coupling Reaction for the Synthesis of Polyunsaturated Macrolactones

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Abstract: A general strategy for the construction of macrocyclic lactones containing conjugated *Z,Z*-1,3-diene subunits is described. The centerpiece of the strategy is a sequential ring-closing metathesis (RCM) that forms an unsaturated siloxane ring, followed by an intramolecular cross-coupling reaction with a pendant alkenyl iodide. A highly modular assembly of the various precursors allowed the preparation of unsaturated macrolactones containing 11-, 12-, 13-, and 14-membered rings. Although the RCM process proceeded uneventfully, the intramolecular cross-coupling required extensive optimization of palladium source, solvent, fluoride source, and particularly fluoride hydration level. Under the optimal conditions (including syringe pump high dilution), the macrolactones were produced in 53–78% yield as single stereoisomers. A benzo-fused 12-membered-ring macrolactone containing an *E,Z*-1,3-diene unit was also prepared by the same general strategy. The *E*-2-styryl iodide was prepared by a novel Heck reaction of an aryl nonaflate with vinyltrimethylsilane followed by iododesilylation with ICl.

Introduction

Highly functionalized macrocycles are considered to be privileged structures because their architectures provide specific disposition of functionalities. Not surprisingly, they have found application in supramolecular chemistry¹ and in drug discovery.² In drug development, complex macrocycles have been found to bind selectively to proteins without significant loss in entropy upon binding, and currently more than 100 marketed drugs are derived from macrocycles that, on average, contain greater than 16-membered rings.^{2a} The drug-like properties of macrocycles notwithstanding, this class of molecules is still under-explored, largely because of concerns about the difficulty of their synthesis.² Nevertheless, a number of macrocycles are in preclinical and clinical development. From a chemical perspective, the continuing discovery of macrocycles of natural origin that possess both complex structures and sensitive functional groups in a compact 12–14-membered macrocycle calls for the development of newer, more efficient methods.

Recently discovered biologically active 12–14-membered macrocycles include the oximidines I³ and III⁴ and the resorcylics⁵ (radicol⁶ and monocilin⁷) that contain a salicylic acid

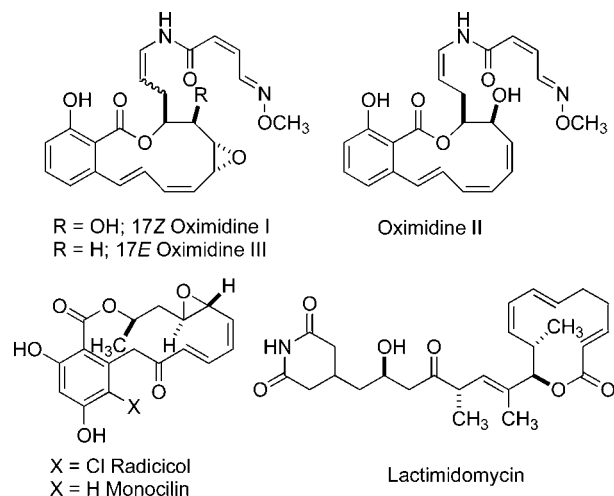


Figure 1. Macrolactone natural products possessing conjugated alkenes.

moiety embedded in a 12-membered macrolide ring (Figure 1). These compounds also possess a conjugated diene or triene moiety within the ring that imparts a high degree of strain within the macrocycle. Efforts to synthesize these and similar lactones have spurred the development of new synthetic methods capable of efficiently constructing these polyunsaturated macrocycles. In addition, examples of natural products with a conjugated diene system that are not salicylic acid derived are known, such as the 14-membered lactone lactimidomycin.⁸

The construction of medium- (8- to 11-membered) and large-ring (>12-membered) macrocycles is generally difficult to

- (1) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796–814.
- (2) (a) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608–624. (b) Harvey, A. L. *Drug Discovery Today* **2008**, *13*, 894–901. (c) Butler, M. S. *Nat. Prod. Rep.* **2008**, *25*, 475–516. (d) Butler, M. S. *Nat. Prod. Rep.* **2005**, *22*, 162–195.
- (3) Kim, J. W.; Shin-Ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153–155.
- (4) Hayakawa, Y.; Tomikawa, T.; Shin-ya, K.; Arai, N.; Nagai, K.; Suzuki, K.; Furihata, K. *J. Antibiot.* **2003**, *56*, 905–908.
- (5) Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22–36.
- (6) Delmotte, P.; Delmotte-Plaquee, J. *Nature* **1953**, *171*, 344.
- (7) Ayer, W. A.; Lee, S. P.; Tsuneda, A.; Hiratsuka, Y. *Can. J. Microbiol.* **1980**, *26*, 766–773.

- (8) Sugawara, K.; Nishiyama, Y.; Toda, S.; Komiyama, N.; Hatori, M.; Moriyama, T.; Sawada, Y.; Kamei, H.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1433–1441.

achieve because of entropy and enthalpic contributions.^{9,10} To overcome these contributions in macrocyclic synthesis, three modes of cyclization are commonly used, and they are distinguished by the position of the reacting groups: (1) the end-to-end, (2) the end-to-backbone, and (3) the backbone-to-backbone cyclizations.¹¹ To favor cyclization over oligomerization, high dilution is effected in one of two ways: (1) the reaction is run in a large volume of solvent to make a very dilute solution, or (2) the precursor is added slowly over a long period time into a given volume of solvent to maintain a high dilution of the compound being cyclized. Pioneering kinetic studies done by Galli and Mandolini on effective molarity (EM) now make it possible to determine the optimal concentration required to favor cyclization.¹²

The methods used to form macrocycles can be broadly classified into two categories: (1) carbon–heteroatom-based cyclization and (2) the carbon–carbon-based cyclization. The carbon–heteroatom-based cyclization to build macrolactams and macrolactones was reported first, and since then, many methods of hydroxy acid lactonization or amino acid lactamization that use different activating groups have been developed.¹³ In addition, lactone formation via π -allylpalladium intermediates has been reported.¹⁴ Cyclization via a carbon–carbon-based strategy initially began with nucleophile- and electrophile-promoted methods,⁹ and later radical- and metal-catalyzed cyclizations appeared.¹⁵ More recently, metal-catalyzed cyclizations have been performed using ring-closing metathesis (RCM).¹⁶ For example, a ruthenium-catalyzed RCM has been applied in a large-scale production of a 15-membered macrocyclic drug candidate.¹⁷ In addition, a major breakthrough in RCM synthesis of macrolactones has been the ring-closing enyne-yne metathesis^{18a} that, in a stereocontrolled process, furnishes a 1,3-diene motif within a macrocycle and consequently has been applied in total synthesis.^{18b,c} Another carbon–carbon-based macrocyclization technique is the palladium-catalyzed cross-coupling reaction, such as the Stille, Suzuki, and Hiyama reactions. The earliest examples of cross-

coupling reactions in macrocyclization employed organoboranes¹⁹ or organostannanes²⁰ as the metallic donor because they were stable and readily prepared. However, the use of organotin has been limited because of tin toxicity, and as a result, recent reports have focused on using organoboron donors²¹ or other donors, such as silicon. The organosilicon-based partners have emerged as competent donors in the synthesis of medium-ring macrocyclic ethers^{22a} and in the total synthesis of cyclic natural products.^{22b}

Background

The dominance of palladium catalysis in organic synthesis is largely due to its specificity and functional group tolerance, allowing the planning and execution of complex molecule total synthesis.²³ Among the earliest reports of a palladium-catalyzed macrocyclization was the palladium-catalyzed intramolecular alkylation of π -allylpalladium complexes with sulfone-stabilized anions.²⁴ The reaction affords medium- to large-ring macrolactones in good yields and has been applied as the key step in total syntheses of natural products.²⁵ Other reports of nucleophilic addition to π -allylpalladium complexes to form macrocycles and macrolactone natural product have appeared.¹⁴

Similarly, the assembly of macrocycles by palladium-catalyzed cross-coupling is emerging as a viable alternative. Since the first report¹⁹ that used haloalkenylboranes to synthesize the sesquiterpene humulene, other palladium-catalyzed cross-coupling reactions of organoboranes have been used to construct complex natural products.²¹ At the same time that palladium-

- (9) (a) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125–4149. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777–2849.
- (10) (a) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1–111. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.
- (11) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491–524.
- (12) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117–3125, and references cited therein.
- (13) (a) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911–939. (b) Hamada, Y.; Shioiri, T. *Chem. Rev.* **2005**, *105*, 4441–4482. (c) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem.* **2005**, *243*, 137–184. (d) Yet, L. *Chem. Rev.* **2003**, *103*, 4283–4306. (e) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767–9822. (f) For an example of macrocyclization by oxidative allylic transposition, see: Jung, H. H.; Seiders, J. R.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8464–8467.
- (14) (a) Rousseau, G.; Homsy, F. *Chem. Soc. Rev.* **1997**, *26*, 453–461. (b) Stang, E. M.; White, M. C. *Nature Chem.* **2009**, *1*, 547–551.
- (15) Edmonds, D. J.; Johnston, D.; Procter, D. P. *Chem. Rev.* **2004**, *104*, 3371–3403.
- (16) (a) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783–3816. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (c) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. (d) Majumdar, K. C.; Rahaman, H.; Roy, B. *Curr. Org. Chem.* **2007**, *11*, 1339–1365. (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527. (f) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.
- (17) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, *9*, 513–515.
- (18) (a) Lacombe, F.; Radkowski, K.; Seidel, G.; Fürstner, A. *Tetrahedron* **2004**, *60*, 7315–7324. (b) Fürstner, A.; Turet, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3462–3466. (c) Fürstner, A.; Bonnekessel, M.; Blank, J. T.; Radkowski, K.; Seidel, G.; Lacombe, F.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2007**, *13*, 8762–8783.
- (19) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1984**, *25*, 761–764.
- (20) (a) Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785–3786. (b) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261–268. (c) Dunctun, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin. Trans.* **1999**, *1*, 1235–1246. (d) Smith, A. B., III; Condon, S. M.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E. *J. Am. Chem. Soc.* **1995**, *117*, 5407–5408.
- (21) For selected examples of alkene–alkene Suzuki macrocyclizations, see: (a) Ghidu, V. P.; Wang, J. Q.; Wu, B.; Liu, Q. S.; Jacobs, A.; Marnett, L. J.; Sulikowski, G. A. *J. Org. Chem.* **2008**, *73*, 4949–4955. (b) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 2722–2723. (c) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760–1768. (d) Molander, G. A.; Dehmelt, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318. (e) Wu, B.; Liu, Q.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6673–6675. For selected examples of aryl–aryl Suzuki macrocyclizations, see: (f) Roberts, T. C.; Smith, P. A.; Cirz, R. T.; Romesberg, F. E. *J. Am. Chem. Soc.* **2007**, *129*, 15830–15838. (g) Lepine, R.; Zhu, J. P. *Org. Lett.* **2005**, *7*, 2981–2984. (h) Kaiser, M.; Siciliano, C.; Assfalg-Machleidt, I.; Groll, M.; Milbradt, A. G.; Moroder, L. *Org. Lett.* **2003**, *5*, 3435–3437. (i) Carbonnelle, A. C.; Zhu, J. P. *Org. Lett.* **2000**, *2*, 3477–3480.
- (22) (a) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 2102–2103. (b) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 15196–15197. (c) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440. (d) Denmark, S. E.; Yang, S.-M. In *Strategies and Tactics in Organic Synthesis*; Harmata, M. A., Ed.; Elsevier: Amsterdam, 2005; Vol. 6, Chapter 4.
- (23) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.
- (24) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867–3868. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1595–1597. (c) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743–4763.
- (25) (a) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552–4553. (b) Trost, B. M.; Ohmori, M.; Boyd, S. A.; Okawara, H.; Brickner, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8281–8284. (c) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825. (d) Marshall, J. A.; Andrews, R. C.; Lebioda, L. *J. Org. Chem.* **1987**, *52*, 2378–2388. For reviews see: (e) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975–1015. (f) Trost, B. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 1173–1192.

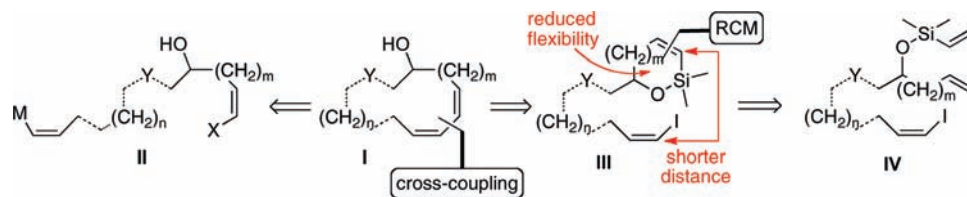


Figure 2. Sequential RCM/silicon-assisted cross-coupling strategy.

catalyzed cross-coupling with organoboranes and organostannanes was being developed, examples illustrating the use of organosilicon in the synthesis of macrocycles appeared. Lastly, macrocycles have also been synthesized by palladium-catalyzed cross-coupling of alkynes.²⁶

The RCM reaction¹⁶ has revolutionized the synthesis of macrocyclic products. Both molybdenum²⁷ (Schrock) and ruthenium²⁸ (Grubbs) complexes have been used to good advantage. Because of their functional group tolerance, ruthenium catalysts are preferred for the synthesis of natural and unnatural products. However, in substrates containing electron-deficient dienes and/or sterically encumbered double bonds, the more reactive molybdenum catalysts are used.

Clearly, both palladium-catalyzed cyclizations and RCM reactions enable synthetic strategies for the total synthesis of macrocyclic natural products. Therefore, the amalgamation of these reactions into a tandem sequence should open new and highly simplifying strategies for the synthesis of macrocycles. Recent disclosures from these laboratories have described a sequential, ring-closing metathesis/silicon-assisted intramolecular cross-coupling reaction for the synthesis of medium-sized rings (9–12) containing a *cis,cis*-diene motif as well as a 9-membered-ring ether that culminated in a total synthesis of (+)-brasilenyne.²² The advantages of this approach for macrocycle synthesis are illustrated in Figure 2. To accomplish the strategic disconnection between the double bonds of a generic macrocyclic polyene **I** with a cross-coupling reaction, the acyclic precursor **II** must be constructed, and the reactive termini bearing X and M must locate each other under catalysis by a transition metal. By constraining one double bond in a smaller ring, the cross-coupling precursor **III** is less flexible and the distance between the reacting termini is reduced, thus favoring macrocyclization. Moreover, the size and substitution of the smaller ring can be easily adjusted in the preparation of RCM precursor **IV**.

Although this process provided efficient access to medium-ring ethers, the general applicability and transferability of this chemistry to the synthesis of larger rings as well as the assembly of the more sensitive macrolactones is still unknown. As an extension of scope, the synthesis of medium- to large-ring (11- to 14-membered) lactones was targeted as a proving ground. This challenge becomes even more formidable when the

flexibility of a macrocycle is constrained by multiple degrees of unsaturation. For example, the assembly of the oximidine **II** core by either ruthenium-catalyzed metathesis²⁹ or Suzuki cross-coupling^{21d} afforded the *E,Z,Z*-triene macrocycles **V** and **VI** in 48% and 42% yields, respectively (Figure 3, entries 1 and 2). On the other hand, the synthesis of a simpler substrate under Mitsunobu conditions (Figure 3, entry 3) afforded the macrocycle **VII** in 23% yield.³⁰

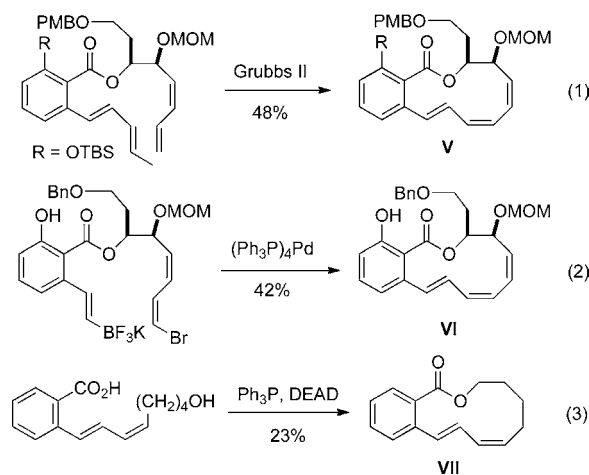


Figure 3. Methods applied to synthesize benzo-fused lactones.

The benzo-fused lactone **VII**, while simple in appearance, was an especially attractive target for a sequential RCM cross-coupling sequence because it contains the conjugated diene motif within the lactone core. The formation of the constrained macrocycle **III** under palladium catalysis was envisioned to proceed via a larger-ring organopalladium intermediate. Because the carbon–palladium–carbon bonds in the intermediate are longer than carbon–carbon bonds, the intermediate would have less strain than the product being formed.^{21d} Facile reductive elimination simultaneously afforded the desired lactone and regenerated the catalyst. The ultimate end goal now became the efficient assembly of an embellished lactone **III** analogue.

Research Plan

In contrast to the use of the RCM/cross-coupling sequence for the synthesis of medium-sized macrocyclic ethers, the assembly of large-ring lactones such as **VII** presents additional problems to unite the reacting ends of the now longer acyclic chain. For example, because of the basic nature of fluoride, tetrabutylammonium fluoride (TBAF)-assisted intramolecular cross-coupling may lead to the cleavage of the lactone. In addition, lactone **VII** possesses a *trans,cis*-diene system conjugated to a benzene ring that causes the compound to behave as a conjugated triene system that is inherently more rigid, and

(26) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485–488.

(27) (a) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; Oregan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378–8387. (b) Bazan, G. C.; Oskam, J. H.; Cho, H. N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907. (c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; Oregan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

(28) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (d) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T. L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.

(29) Wang, X.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 6040–6041.

(30) Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487–3490.

thus it is more difficult to fuse the reacting termini. Of these problems, the greater ring size and the lability of the ester group in the basic TBAF reaction medium were potentially most challenging and thus led to the investigation of lactones **VIII** (Figure 4) that are easier to access and modify. These lactones were chosen because they addressed the consequences of placing the carboxyl and hydroxyl groups in different locations with respect to the diene moiety. Various ring sizes of **VIII** could be accessed from the cyclic siloxanes such as **IX**. The strategy to use cyclic siloxanes **IX** was chosen to fix one end of the macrocycle to be formed in a smaller ring to reduce both flexibility and distance between the two reacting termini. The siloxane **IX** would be derived from RCM of silyl ethers **X**. The silyl ethers **X** could be elaborated with ease from diols **XI** and the acid **XII**. The key step in this route is the sequential ring-closing metathesis/intramolecular cross-coupling reaction.

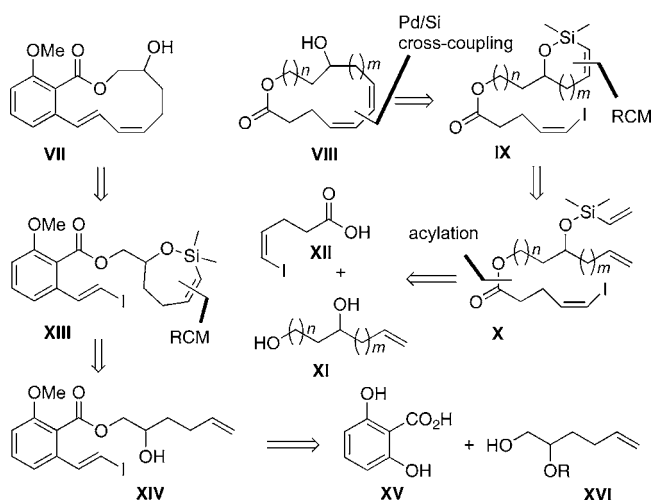


Figure 4. General synthetic sequence for the construction of macrolactones.

The conjugated triene problem will be investigated by the synthesis of siloxane **XIII** from alcohol **XIV**. Alcohol **XIV** in turn would arise from elaboration of 2,6-dihydroxybenzoic acid (**XV**) and alcohol **XVI**. We describe herein the successful implementation of this plan, which culminated in the syntheses of medium- to large-ring macrolactones **VIII** and the fused benzolactone **VII**.

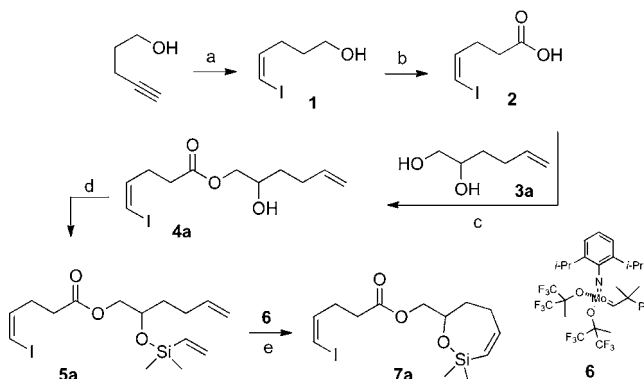
Results

To initiate the study of the silicon-assisted cross-coupling macrocyclization, an efficient and versatile synthetic sequence was needed to generate the cycloalkenylsiloxanes **7a–e** (Schemes 1 and 3) and **10** (Scheme 5) in high yield. The cyclic alkenylsiloxanes were prepared in seven steps from 4-pentyn-1-ol. The synthesis of the styryl siloxane **10**, on the other hand, required eight steps. The selection of the reaction sequence was guided by the stability of the products along each pathway. Because the silyl ethers and the siloxanes are sensitive compounds, the syntheses of these products were designed such that they are the last compounds prepared prior to macrocyclization. The details of each synthetic sequence are described below.

1. Preparation of Alkenylsiloxane 7a. Siloxane **7a** (the cross-coupling precursor used for optimization) was prepared from 4-pentyn-1-ol as depicted in Scheme 1. Iodination of 4-pentyn-1-ol with iodine in aqueous KOH furnished 5-iodo-4-pentyn-1-ol that was immediately subjected to a selective cis reduction

with diimide³¹ generated in situ from potassium azodicarboxylate,³² to afford (*Z*)-5-iodo-4-pentyn-1-ol (**1**)³³ in 62% yield over two steps. Alcohol **1** was then oxidized by a CrO₃-catalyzed periodate oxidation³⁴ to form (*Z*)-5-iodopent-4-enoic acid (**2**)³³ in 97% yield. Hex-5-ene-1,2-diol (**3a**) was synthesized from glycidol following the established sequence.³⁵

Scheme 1^a



^a Conditions: (a) 1. I₂, KOH, MeOH; 2. KO₂CN=NCO₂K, AcOH, THF/*i*-PrOH, (62%); (b) CrO₃/H₅IO₅, MeCN/H₂O (9/1), (97%); (c) 1. COCl₂, benzene; 2. **3a**, collidine, CH₂Cl₂, -78 °C, (79%); (d) chlorodimethylvinylsilane, Et₃N, CH₂Cl₂ (93%); (e) **6**, benzene, rt (87%). The yields are of analytically pure material.

Acid **2** was converted to its acid chloride, and the crude acid chloride solution was added dropwise to a solution of diol **3** and collidine³⁶ in dichloromethane at -78 °C to afford ester **4a** in 79% yield over two steps. Silylation of ester **4a** with chlorodimethylvinylsilane gave the sensitive silyl ether **5a** in 93% yield after purification with silica gel buffered with 1% triethylamine. The alkenylsilyl ether **5a** was then subjected to RCM using the Schrock molybdenum carbene complex **6**²⁷ to afford the alkenylsiloxane **7a** in 87% yield.

2. Optimization of the Intramolecular Cross-Coupling Reaction. With alkenylsiloxane **7a** in hand, the palladium-catalyzed intramolecular cross-coupling was attempted using the reaction conditions previously developed in these laboratories, namely, allylpalladium chloride dimer (APC) as the catalyst and tetrabutylammonium fluoride trihydrate (TBAF·3H₂O) as the activator.²² The reaction was carried out under high dilution such that a 0.1 M solution of siloxane **7a** was slowly added using a syringe-pump into a mixture of APC (0.1 equiv) and a 1 M solution of TBAF·3H₂O in THF (10 equiv) over a 40 h period at room temperature. At the 10 h time point, precipitation of palladium black was observed. After 40 h, ¹H NMR analysis of the reaction mixture showed traces of opened siloxane and hydrolyzed silyl ether products.

The presence of palladium black implied that catalyst death was occurring during the extended reaction time. To determine if catalyst death was caused by oxygen poisoning, the reaction was repeated under the same conditions but in a Schlenk flask instead of a three-necked, round-bottomed flask. In this case

(31) Luthy, C.; Konstantin, P.; Untch, K. G. *J. Am. Chem. Soc.* **1978**, *100*, 6211–6217.

(32) Groves, J. T.; Ma, K. W. *J. Am. Chem. Soc.* **1977**, *99*, 4076–4082.

(33) Wu, Y.; Gao, J. *Org. Lett.* **2008**, *10*, 1533–1536.

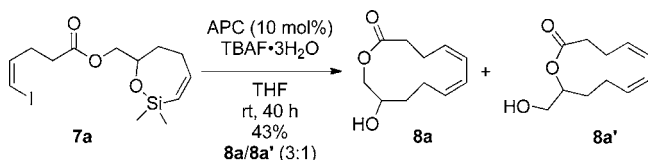
(34) Zhao, M. Z.; Li, J.; Song, Z. G.; Desmond, R.; Tschäen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323–5326.

(35) Pospisil, J.; Marko, I. E. *Tetrahedron Lett.* **2006**, *47*, 5933–5937.

(36) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791–3793.

the desired lactone **8a** was isolated together with an isomeric lactone **8a'** as an inseparable 3:1 mixture in 43% yield (Scheme 2). The identity and ratio of **8a/8a'** were determined by ¹H NMR analysis.³⁷ Further structural evidence was secured by converting the components to their triethylsilyl (TES)-protected ethers followed by exposure of the mixture to CrO₃·2py oxidation,³⁸ which converted the primary TES-protected **8a'** to an aldehyde while the TES-protected secondary alcohol **8a** was recovered intact.³⁷ The isomeric lactone **8a'** most likely arose from a base-promoted transesterification initiated by the fluoride ion. Accordingly, further optimization was needed to suppress this undesired process and increase the yield of the desired product.

Scheme 2



2.1. Optimization of TBAF Hydration Level and Solvent. Operating under the hypothesis that the isomeric lactone **8a'** arose from **8a** because of the basic character of TBAF, measures to lower its basicity while maintaining fluoride anion strength were taken. Detailed studies of the nucleophilicity of quaternary ammonium fluorides have shown that the trihydrated fluoride anion is both very basic and nucleophilic.³⁹ These properties can be attenuated with protic solvents and modulated by varying the hydration level of the quaternary ammonium salt. This strategy was critical for the successful cross-coupling of silanols with aryl triflates⁴⁰ and alkenyl iodides.⁴¹ To address the problem of ester hydrolysis, two experiments were performed. The fluoride source (TBAF·3H₂O) was further hydrated by adding the appropriate amounts of water to a 1 M solution of TBAF·3H₂O in THF to form solutions of TBAF·4H₂O and TBAF·6H₂O. The palladium-catalyzed macrocyclization reaction using the TBAF·4H₂O afforded a higher yield of product (64%), but again as a 3:1 mixture of lactones **8a** and **8a'**, whereas the reaction with TBAF·6H₂O produced the macro-lactones in a slightly lower yield of 59% (Table 1, entries 3 and 4). Higher hydration levels, TBAF·10H₂O and TBAF·15H₂O, gave lower yields (46% and 39%, respectively) but afforded excellent selectivity, only macrocycle **8a** being formed (Table 1, entries 10 and 11). TBAF·6H₂O was chosen as the fluoride source in the next stage of optimization because of its lower fluoride anion strength.³⁹

The problem of post facto isomerization was addressed by adjusting the amount of TBAF·6H₂O. Lowering the TBAF·6H₂O loading from 10 to 5 equiv improved the yield significantly to 72%, but the ratio of the two isomers **8a** and **8a'** remained the same (Table 1, entry 5). However, when the amount of TBAF·6H₂O was reduced to 2.5 equiv, the macro-lactones **8b** and **8b'** were isolated in only 26% yield (Table 1, entry 6). For the purpose of further optimization, 5 equiv of TBAF·6H₂O was selected.

Table 1. Optimization of the Fluoride Source and Solvent for the Macrocyclization^a

entry	fluoride source	equiv	solvent	8a + 8a'	
				yield, %	ratio ^b
1	TBAF·3H ₂ O	10	THF	0	
2	TBAF·3H ₂ O	10	THF	43	3:1
3	TBAF·4H ₂ O	10	THF	64	3:1
4	TBAF·6H ₂ O	10	THF	59	3:1
5	TBAF·6H ₂ O	5	THF	72	3:1
6	TBAF·6H ₂ O	2.5	THF	26	3:1
7	TBAF·6H ₂ O	5	dioxane	76	3:1
8	TBAF·6H ₂ O	5	DMF	84	2:1
9	TBAF·7H ₂ O	5	DMF	79	2:1
10	TBAF·10H ₂ O	5	THF	46	100:0
11	TBAF·15H ₂ O	5	THF	39	100:0

^a Reaction conditions employed 0.25 mmol of **7a** at 0.1 M. ^b Ratio determined by ¹H NMR analysis.

Because the reaction optimization up to this juncture had been conducted with an ethereal solvent (THF), dioxane was selected next because it is a competent solvent for alkenyl–alkenyl cross-coupling reactions.⁴⁰ The use of dioxane led to an increase in yield (76%) of the macrocycles (Table 1, entry 7). This result suggested that solvent polarity may have an effect on product yield because dioxane is marginally more polar than THF [dioxane ($A_j + B_j$) = 0.86 versus THF ($A_j + B_j$) = 0.84].⁴² The use of DMF [($A_j + B_j$) = 1.23] led to a still higher yield of the macrocycles **8a** and **8a'** (84%) but lower selectivity (2:1 ratio) (Table 1, entry 8). Because DMF afforded the macrolactones **8a** and **8a'** in higher yield compared to THF or dioxane, it was selected as the solvent of choice going forward.⁴³

2.2. Survey of Fluoride Sources. Many fluoride sources are commercially available or are easily accessed in a few synthetic steps. The survey of fluoride sources other than TBAF·6H₂O began with the commercially available tetramethylammonium fluoride tetrahydrate (TMAF·4H₂O). This salt is superior to TBAF·3H₂O in the cross-coupling of aryl triflates and alkenyl-silanols.⁴⁰ Tetramethylammonium is the smallest of all tetralkylammonium cations and has a symmetrical, almost spherical structure.⁴⁴ By adapting the conditions developed previously, but now with TMAF·4H₂O as the fluoride source, the cross-coupling of siloxane **7a** afforded macrocycle **8a** as a single isomer, albeit in only 47% yield (Table 2, entry 1). Increasing the hydration level to TMAF·6H₂O afforded the cross-coupled product in 34% yield (Table 2, entry 2). Despite the low yields of **8a** obtained with TMAF·6H₂O, the high selectivity was particularly attractive and encouraged further study.

Benzyltrimethylammonium fluoride (BTMAF) is a close analogue of TMAF and was easily prepared from benzyltri-

(37) See Supporting Information for details.

(38) Smith, A. B., III; Lupo, A. T.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648–6656.

(39) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1989**, *54*, 328–332.

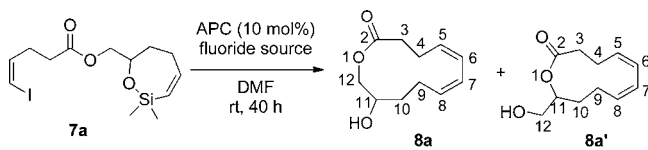
(40) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771–3774.

(41) Denmark, S. D.; Liu, J. H.-C.; Muhuhi, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 14188–14189.

(42) Reichardt, C. *Solvents and Solvents Effects in Organic Chemistry*, 3rd updated and enlarged ed.; Wiley-VCH: Weinheim, 2003; Chapter 7. A_j represents acidity, a solvent anion-solvating tendency, while B_j represents basicity, a solvent cation-solvating tendency. The sum of acidity and basicity is a solvent solvation capability or its polarity.

(43) The DMF used in these investigations was dried by percolation through an activity 1 alumina bed. The water content was determined by triplicate Karl Fischer titration to be 3.3 μg/100 μL, or 33 ppm.

(44) Harmon, K. M.; Gennick, I. *Inorg. Chem.* **1975**, *14*, 1840–1845.

Table 2. Survey of the Fluoride Sources for the Macrocyclization^a


entry	fluoride source	solvent	equiv	8a + 8a'	
				yield, %	ratio ^b
1	TMAF·4H ₂ O	DMF	5	47	100:0
2	TMAF·6H ₂ O	DMF	5	34	100:0
3	BTMAF	DMF	5	39	2:1
4	BTMAF·6H ₂ O	DMF	5	49	6:1
5	BTMAF·10H ₂ O	DMF	5	0	
6	TEAF·2H ₂ O	DMF	5	32	2:1
7	TEAF·6H ₂ O	DMF	5	40	2:1
8	TBAT	THF	5	29	100:0
9	TASF	THF	5	22	100:0
10	CsF	DMF	5	0	

^a Reaction conditions employed 0.25 mmol of **7** at 0.1 M. ^b Ratio determined by ¹H NMR.

methylammonium hydroxide in 73% yield.⁴⁵ The use of BTMAF (with hydration assumed to be <0.5 after drying)⁴⁶ in the macrocyclization reaction of **7a** afforded the macrocycles **8a** and **8a'** in 39% yield in a 2:1 ratio (Table 2, entry 3). To suppress the isomerization, hydrated BTMAF was used (BTMAF·6H₂O), and the product was formed in higher yield (49% versus 39%) and improved selectivity (6:1 versus 2:1) (Table 2, entry 4). Unfortunately, increasing the hydration level to BTMAF·10H₂O was not productive (Table 2, entry 5).

Next, the commercially available tetraethylammonium fluoride dihydrate (TEAF·2H₂O) was investigated. With this activator, the desired macrocycle was obtained in a 32% yield as a 2:1 ratio of **8a** and **8a'** (Table 2, entry 6). Increasing the hydration level to TEAF·6H₂O gave a modest increase in yield of **8a** and **8a'** (40%), but the selectivity remained the same (Table 2, entry 7).

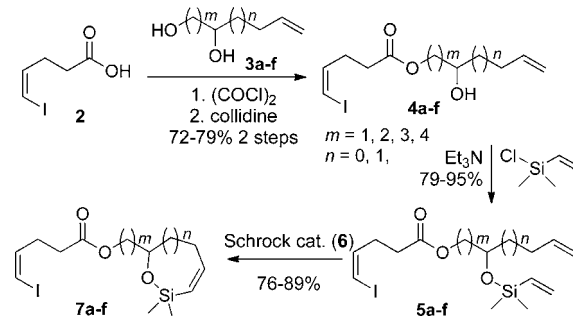
The last phase of this survey was the investigation of anhydrous fluoride sources. A number of anhydrous fluoride sources have been used for silicon-based cross-coupling, such as tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF),⁴⁷ tetrabutylammonium triphenyldifluorosilicate (TBAT),⁴⁸ and cesium fluoride (CsF).⁴⁹ Reaction of siloxane **7a** with TBAT afforded the macrocycle **8a** in 29% yield as a single isomer (Table 2, entry 8), while the activation with TASF afforded **8a** in 22% and with the same selectivity (Table 2, entry 9). Cesium fluoride led only to decomposition of the starting material, and no macrocycle was detected (Table 2, entry 10).

Integrating all of the optimization data, the combination that employed 0.1 equiv of APC, 5 equiv of TBAF·6H₂O as the fluoride source, and DMF as the solvent was chosen as the optimal conditions because it afforded the highest yield of **8a**. A 1.0-mmol-scale macrocyclization reaction of siloxane **7a** under these conditions after 48 h furnished **8a** and **8a'** in 78%

yield in a 2:1 ratio. The diagnostic alkene resonances of **8a**, namely HC(6) and HC(7), appeared at 6.08 ppm (dd, ³J = 10.8, 7.0 Hz) and 5.98 ppm (dd, ³J = 11.0, 7.0 Hz), respectively. The resonance for H₂C(12) appeared as an ABX quartet at 4.19 ppm (dd, ³J = 11.3, 3.0 Hz) and 3.93 ppm (dd, ³J = 11.5, 5.0 Hz). On the other hand, compound **8a'** displayed a single, well-resolved alkene resonance for HC(6) and HC(7) at 5.88 ppm (d, ³J = 11.0 Hz). The signal for H₂C(12) appeared as an ABX quartet at 3.66 ppm (ddd, ³J = 11.9, 5.8, 3.5 Hz) and 3.55 ppm (dd, ³J = 12.0, 10.0 Hz). All attempts to resolve alkene peaks for HC(5) and HC(8) were not successful,⁵⁰ but to the best of our knowledge the macrolactones are formed in a stereospecific manner.

Preliminary molecular modeling calculations⁵¹ show that **8a** is 0.26 kcal/mol lower in energy than **8a'**, which corresponds to a predicted ratio of 1.6:1 at room temperature, close to the observed ratio of 2:1. Although a good yield of the 12-ring macrolactone could be obtained, it was not possible to suppress the formation of the 11-ring isomer without a substantial decrease in yield. Thus, before further optimization was undertaken, it was deemed prudent to establish if isomerization is a general phenomenon or is unique to this structure. Accordingly, a selection of other precursors was prepared to evaluate the generality of the cross-coupling macrocyclization.

3. Scope of the Intramolecular Cross-Coupling Reaction. To evaluate the scope of this cross-coupling reaction for the construction of macrocycles, the siloxanes **7b–f** (Scheme 3) were synthesized in a fashion similar to that shown for synthesis of siloxane **7a**. The assembly began with the conversion of acid **2** to the acid chloride that was then added dropwise to cooled solutions of known diols **3b–f**⁵² in collidine to provide esters **4b–f** in 72–79% yields (Table 3). The esters were converted to their respective silyl ethers **5b–f** and then subjected to RCM with catalyst **6** as before to afford siloxanes **7b–f**.

Scheme 3

The scope of the intramolecular cross-coupling reaction was investigated on a 1.0 mmol scale under the optimized reaction conditions (0.1 equiv of APC and 5 equiv of TBAF·6H₂O in DMF (0.1 M) using syringe pump addition at room temperature).

(45) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025–1030.

(46) (a) Cox, D. F.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216–3219. (b) Albanese, D.; Landini, D.; Penso, M. *J. Org. Chem.* **1998**, *63*, 9587–9589.

(47) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918–920.

(48) (a) DeShong, P.; Handy, C. J.; Mowery, M. E. *Pure Appl. Chem.* **2000**, *72*, 1655–1658. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266–3270.

(49) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153–5159.

(50) All attempts to resolve the olefinic region by recording the ¹H NMR spectra with various deuterated solvents (CDCl₃, CD₂Cl₂, C₆D₆, CD₃OD, toluene-*d*, DMSO-*d*, pyridine-*d*, tetrahydrofuran-*d*, 1,4-dioxane-*d*) and with lanthanide shift reagents (EuFOD and YbFOD) were unsuccessful.

(51) Spartan 08, DFT, B3LYP, 6-31*G.

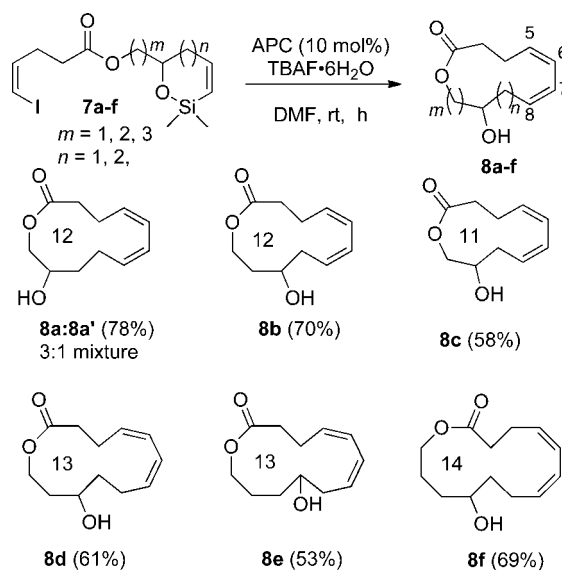
(52) (a) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528–529. (b) Crawford, R. J.; Lutener, S. B.; Cockcroft, R. D. *Can. J. Chem.* **1976**, *54*, 3364–3376. (c) Sugawara, M.; Yoshida, J. *Tetrahedron Lett.* **1999**, *40*, 1717–1720. (d) Nishikawa, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2003**, *59*, 9661–9668. (e) Klos, A. M.; Heintzelman, G. R.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 3758–3761.

Table 3. Preparation of Esters **4**, Silyl Ether **5**, and Siloxanes **7**

<i>m, n</i>	product (yield, %) ^a		
	ester 4	silyl ether 5	siloxane 7
1, 1	4a (79)	5a (93)	7a (87)
2, 0	4b (72)	5b (79)	7b (89)
1, 0	4c (76)	5c (89)	7c (81) ^b
2, 1	4d (70)	5d (90)	7d (84)
3, 0	4e (76)	5e (95)	7e (83)
3, 1	4f (72)	5f (91) ^b	7f (76)

^a Yields of analytically pure material. ^b Yields of chromatographically homogeneous material.

The cyclization of siloxane **7b** was carried out first because the product, 12-membered macrocycle **8b**, had the same ring size as **8a** obtained earlier (Scheme 4). Under the conditions described above, siloxane **7b** afforded macrocycle **8b** in 70% yield as a single isomer. This outcome suggested that the transactonization observed in synthesis of **8a** may be substrate dependent.

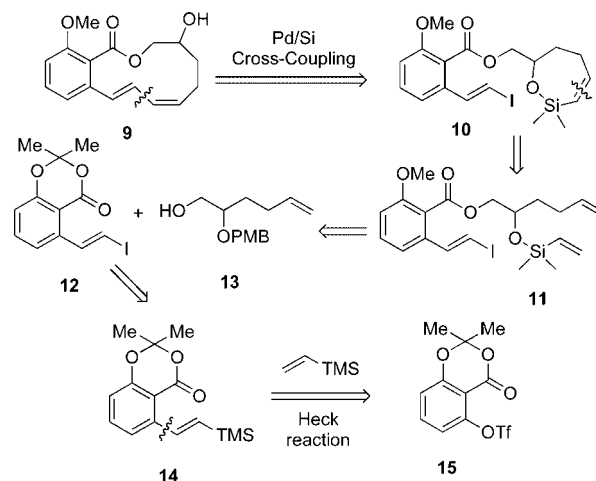
Scheme 4

Gratifyingly, siloxane **7c** afforded the 11-membered macro-lactone **8c** in 58% yield, again as a single isomer. The diagnostic alkene resonances for HC(6) and HC(7) appeared at 6.04 ppm (dd, ³*J* = 9.8, 9.8 Hz). The synthesis of 11-membered macrocycles is known to be more difficult than that of 12-membered rings.¹⁰

Next, this process was extended to the synthesis of 13- and 14-membered rings. Thus, cross-coupling of siloxane **7d** afforded the 13-membered macrocycle **8d** in 61% yield. The closure of this macrolactone required longer reaction time (54 h) compared to that of the 12-membered lactone (40 h). The synthesis of another 13-membered ring, **8e**, that contained a different substitution pattern proceeded in 53% yield after 48 h. Unfortunately, the alkene region of the ¹H NMR spectra of both 13-membered lactones **8d** and **8e** could not be fully analyzed.⁵⁰ Finally, the synthesis of the 14-membered ring **8f** was achieved from siloxane **7f** in 69% yield after 54 h. Gratifyingly, the alkene resonances for HC(6) and HC(7) were well resolved and showed two doublets of doublets at 6.32 ppm (dd, ³*J* = 10.5, 10.5 Hz) and 6.23 ppm (dd, ³*J* = 10.8, 10.8 Hz), respectively.

4. Formation of Benzo-Fused Macrocyclic Diene (E,Z)-9. The success of the intramolecular cross-coupling for the synthesis

of 11-, 12-, 13-, and 14-membered lactones was gratifying and served to demonstrate that this method could be applied in synthesis of natural products that contain the conjugated diene moiety as a part of a macrolactone. However, a more challenging goal was to apply this approach to synthesize a conjugated triene motif. As an extension of the chemistry described above, the synthesis of lactone **9** (Scheme 5) was identified as a model study that could be used to access oximidine III and eventually the triene-conjugated oximidine II natural product.

Scheme 5

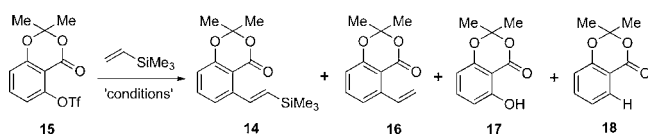
The synthesis of the benzo-fused lactone **9** would result from macrocyclization of the styryl iodide **10** (Scheme 5). The siloxane portion of **10** would arise from elaboration of the silyl ether **11**, itself prepared from coupling of styryl iodide **12** with alcohol **13**. Synthesis of such styryl iodides can be achieved by Takai olefination of aromatic aldehydes,⁵³ halodecarboxylation of cinnamic acids (Hunsdiecker reaction),⁵⁴ reduction of dihaloalkenes,⁵⁵ base-promoted homologation of benzyl bromides,⁵⁶ or ruthenium-catalyzed silylation of styrene.⁵⁷ Although useful, all of the above methods have various drawbacks. A simpler approach would involve the iododesilylation⁵⁸ of vinylsilanes themselves, obtained by either a Mizoroki–Heck⁵⁹ reaction of an aryl halide with vinyltrimethylsilane⁶⁰ or a hydrosilylation of an aryl alkyne⁶¹ obtained from a Sonagashira reaction of an aryl halide. However, in the case at hand, these methods could

- (53) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410. (b) Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, 1268–1270. (c) Haack, T.; Kurtkaya, S.; Snyder, J. P.; Georg, G. I. *Org. Lett.* **2003**, *5*, 5019–5022.
- (54) (a) Kuang, C. X.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* **2005**, 1319–1325. (b) Das, J. P.; Roy, S. *J. Org. Chem.* **2002**, *67*, 7861–7864. (c) You, H.-W.; Lee, K.-J. *Synlett* **2001**, 105–107. (d) Naskar, D.; Roy, S. *Tetrahedron* **2000**, *56*, 1369–1377.
- (55) Horibe, H.; Kondo, K.; Okuno, H.; Aoyama, T. *Synthesis* **2004**, 986–988.
- (56) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5485–5488.
- (57) Pawluc, P.; Hreczycho, G.; Szudkowska, J.; Kubicki, M.; Marciniak, B. *Org. Lett.* **2009**, *11*, 3390–3393.
- (58) (a) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647–8650. (b) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100–1106.
- (59) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.
- (60) (a) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286–5290. (b) Garst, M. E.; McBride, B. J. *J. Org. Chem.* **1989**, *54*, 249–250. (c) Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *J. Organomet. Chem.* **2005**, *690*, 3790–3802.

not be used because a suitable aryl halide precursor to compound **14** is not readily available. An alternative solution was to find conditions that could effect a Mizoroki–Heck⁵⁹ reaction between aryl triflate **15**⁶² and vinyltrimethylsilane.

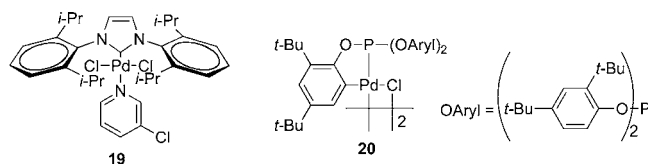
4.1. Optimization of the Mizoroki–Heck Reaction of Vinyltrimethylsilane. To the best of our knowledge, the Mizoroki–Heck reaction of an aryl fluoroalkylsulfonate with vinyltrimethylsilane is unprecedented, and this example represented an even more daunting challenge because of the ortho substituent on aryl triflate **15**.⁶³ The initial survey employed the phosphine-free “Jeffrey conditions”⁶⁴ (Table 4, entry 1). Unfortunately, when run at ambient temperature, the reaction stalled at 43% conversion, but increasing the temperature to 80 °C improved the conversion to 73% (Table 4, entry 2). Changing the solvent to MeCN did not offer any significant improvement (Table 4, entry 3).

Table 4. Optimization of the Heck Reaction of Aryl Triflate **15**^a



entry ^a	Pd source (5 mol % Pd), conditions	yield, % ^b				
		15	14	16	17	18
1 ^c	Pd(OAc) ₂ , <i>n</i> -Bu ₄ NOAc, DMF, rt	57	43			
2	Pd(OAc) ₂ , <i>n</i> Bu ₄ NOAc, DMF	27	73			
3	Pd(OAc) ₂ , <i>n</i> Bu ₄ NOAc, MeCN	30	70			
4	19 , ^d DMF	58	27	15		
5	20 , ^d DMF	71	22	7		
6	Pd(OAc) ₂ , Ph ₃ P, DMF	46	54			
7	Pd(OAc) ₂ , dppf, DMF	27	34	17	22	
8	Pd(OAc) ₂ , BIPHEP, DMF	19	10	71		
9	Pd(OAc) ₂ , <i>t</i> -Bu ₃ P·HBF ₄ , DMF	60				30
10	Pd(OAc) ₂ , <i>t</i> -Bu ₃ P·HBF ₄ , DMSO	74	18			8
11	Pd(OAc)₂, <i>t</i>-Bu₃P·HBF₄, NMP	88				12
12	Pd(OAc) ₂ , BPTBP, ^e DMF	74				16
13	Pd(OAc) ₂ , BPTBP, ^e DMSO	87	3			10
14	Pd(OAc) ₂ , BPTBP, ^e NMP	42	48			19
15	Pd(OAc)₂, BPTBP,^e MeCN	85				10

^a Reaction conditions, unless indicated otherwise, employed 0.25 mmol of **15**, 3 equiv of trimethylvinylsilane, and 2 equiv of Et₃N, 80 °C. ^b Yield for **15** is unreacted starting material. Yields of **14**, **16**, **17**, and **18** were determined by GC analysis without an internal standard. ^c No Et₃N was used as base. ^d Ligands: **VII** and **VIII**. ^e BPTBP = 2-(di-*tert*-butylphosphino)biphenyl.



A survey of Pd sources that represent the three most widely used ligand classes, namely N-heterocyclic carbene (NHC) **19**,^{65–67} phosphite **20**,^{65,68} and phosphines^{65,67} (Table 4, entries 4–6), was carried out. Two important observations were made:

- (61) Hamze, A.; Provot, O.; Brion, J. D.; Alami, M. *J. Organomet. Chem.* **2008**, *693*, 2789–2797.
 (62) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286–5298.
 (63) Neuville, L.; Bigot, A.; Dau, M. E. T. H.; Zhu, J. P. *J. Org. Chem.* **1999**, *64*, 7638–7642.
 (64) (a) Jeffery, T.; Ferber, B. *Tetrahedron Lett.* **2003**, *44*, 193–197. (b) Jeffery, T. *Tetrahedron Lett.* **1999**, *40*, 1673–1676. (c) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

(1) triphenylphosphine (Table 4, entry 6) provided a significantly increased yield compared to **19** and **20** (Table 4, entries 4 and 5), and (2) palladium acetate (Table 4, entry 6) was the best palladium source, affording the desired arylvinylsilane **14** in 54% yield together with a 46% yield of unreacted starting material.⁶⁹ Most importantly, this combination did not lead to the formation of byproducts. Moreover, the reactivity and selectivity of Pd(OAc)₂ can be tuned with different phosphine ligands.

Catalysis of the Heck reaction with palladium complexes bearing electron-rich arylphosphines such as tri-*o*-tolylphosphine [(*o*-Tol)₃P] and 1,2-bis(diphenylphosphino)ferrocene (dppf) often have higher reaction rates and turnovers compared to Ph₃P.⁷⁰ In addition, tri-(*tert*-butyl)phosphine (*t*-Bu₃P) and di(*tert*-butylphosphino)ferrocene are effective ligands for Heck reactions.^{67,71}

Thus, a survey of electron-rich, sterically hindered monodentate and bidentate phosphine ligands was carried out with Pd(OAc)₂. The first reactions were run using the bidentate ligands dppf and BIPHEP (Table 4, entries 7 and 8). The use of dppf (Table 4, entry 7) gave the expected silyl ether **14** in 34% yield together with 27% yield of unreacted starting material **15**. In addition, the desilylated compound **16** and the hydrolysis byproduct **17** were observed in 17% and 22% yields, respectively. The ligand BIPHEP, on the other hand, gave the desilylated product **16** in 71% yield and only 10% yield of the desired material **14**. Clearly, bidentate ligands were inferior to Ph₃P, so monodentate ligands were surveyed next.

To evaluate *t*-Bu₃P, the commercially available tri-*tert*-butylphosphine tetrafluoroborate salt (*t*-Bu₃P·HBF₄) was employed, and complete consumption of the starting material occurred to afford **14** in 60% yield together with reduction product **18** in 30% yield; however, no other byproducts were detected by GC analysis (Table 4, entry 9). The formation of reduced products is known in cross-coupling reactions, particularly in DMF with tertiary amines.⁷² To remedy this problem, both DMSO and NMP were tested (Table 4, entries 10 and 11). The use of DMSO increased the yield of **14** to 74% yield together with 11% of **8** but also led to formation of the hydrolyzed product **17** in 18% yield. The use of NMP led to an increase in yield of **14** (88%), albeit with 12% yield of **18**.

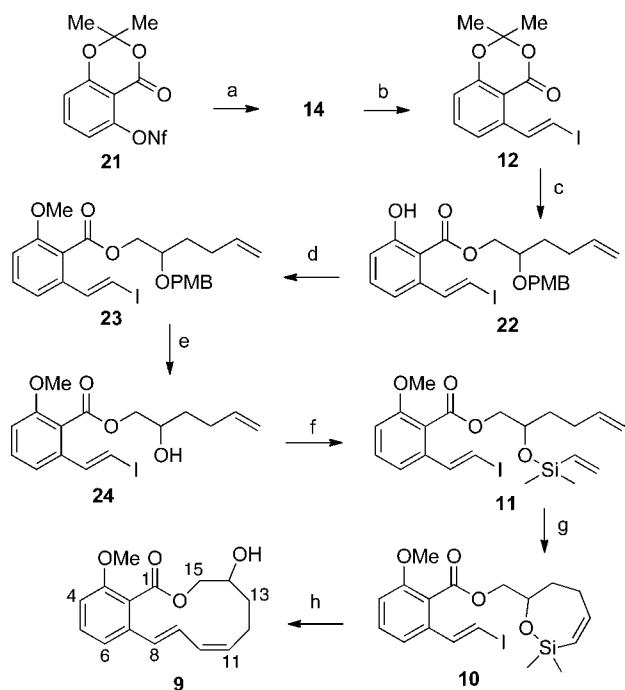
On the other hand, the use of 2-(di-*tert*-butylphosphino)biphenyl (BPTBP) in DMF gave **14** in 74% yield together with **18** in 12% yield, a significantly better result than that obtained with the use of *t*-Bu₃P and DMF (Table 4, entry 12). Moreover, DMSO led to the formation of **14** in 87% yield together with **18** (10%) and **17** (3%) (Table 4, entry 13). In NMP, the reaction stalled, and **18** was obtained in 48% yield accompanied by a 10% yield of **18**

- (65) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
 (66) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309.
 (67) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
 (68) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055–4082.
 (69) (PPh₃)₂PdCl₂ afforded **14** (49%) and **16** (38%) along with 15% of recovered **15**.
 (70) Qadir, M.; Mochel, T.; Hii, K. K. *Tetrahedron* **2000**, *56*, 7975–7979.
 (71) (a) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123–2132. (b) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 5842–5843.
 (72) (a) Ghosez, L.; Franc, C.; Denonne, F.; Cuisinier, C.; Touillaux, R. *Can. J. Chem.* **2001**, *79*, 1827–1839. (b) Handy, S. T.; Bregman, H.; Lewis, J.; Zhang, X. L.; Zhang, Y. N. *Tetrahedron Lett.* **2003**, *44*, 427–430.

and a 42% recovery of the starting material **15** (Table 4, entry 14). However, upon using MeCN, **14** was obtained in 85% yield together with a 10% yield of the reduced product **10**.

From the ligand and solvent survey conducted above, the reaction conditions that employed *t*-Bu₃P·HBF₄ in NMP and BPTBP in MeCN were identified as the best ligand/solvent combinations that gave the highest yields of **14** without creating more than one byproduct. However, of the two ligands employed, BPTBP was chosen for scale-up because the reaction appeared to be cleaner by GC analysis. On a 1.3-mmol scale this reaction afforded the desired arylvinylsilane **14** in 66% yield after chromatographic purification.

Among the optimization studies, entry 6 in Table 4 was intriguing because, aside from the Jeffery conditions, this was the only reaction that did not give byproducts. This result indicated that a more reactive electrophile might be a better substrate. Accordingly, an aryl nonaflate, known to be 1.4 times more reactive⁷³ than the corresponding aryl triflate, was tested. The desired aryl nonaflate **21** (Scheme 6) was efficiently prepared in 88% yield from the corresponding phenol.⁷⁴ Subjecting **19** to the reaction conditions in Table 4, entry 6, afforded a single product by GC analysis. On a 10-mmol scale this reaction yielded the analytically pure arylvinylsilane **14** in 84% yield after chromatography and Kugelrohr distillation (Scheme 6).

Scheme 6^a

^a Conditions: (a) Pd(OAc)₂ (5 mol %), Ph₃P (10 mol %), chlorodimethylvinylsilane, Et₃N, MeCN, 80 °C (84%); (b) ICl, MeCN, 0 °C (83%); (c) **13**, Otera catalyst, toluene, reflux (89%); (d) CH₃I, Cs₂CO₃, THF (96%); (e) CAN, MeCN/H₂O (86%); (f) chlorodimethylvinylsilane, Et₃N, CH₂Cl₂ (93%); (g) **6**, benzene, rt (83%); (h) [allyl]PdCl₂ (10 mol %), TBAF·6H₂O, DMF (74%).

Now with a robust and easily scaled process for synthesizing arylvinylsilane **14** in hand, the elaboration to the macrocyclization precursor siloxane **10** began in earnest.

4.2. Synthesis of the Benzo-Fused Macrolactone (E,Z)-9. Iododesilylation of **14** with ICl⁵⁸ afforded arylvinyl iodide **12** in 83% yield with complete retention of the double bond configuration (Scheme 6). Attempts to open lactone **12** with the

sodium or potassium alkoxide of **13**⁷⁴ (Scheme 5) failed and led to vinyl iodide decomposition and/or inconsistent conversion to the expected ester **22**. Similarly, attempts to effect acylation with titanium(IV) isopropoxide⁷⁵ met with failure. However, acylation using 1-hydroxy-3-(isothiocyanato)tetrabutyl-distannoxane (Otera's catalyst)⁷⁶ in toluene at reflux furnished the analytically pure ester **22** in 89% yield after chromatography. Methylation of the hydroxyl group of **22** with methyl iodide and Cs₂CO₃ afforded **23** in 96% yield. Removal of the PMB group was then effected using ceric ammonium nitrate (CAN) to afford alcohol **24** in 86% yield. Alcohol **24** was then silylated with chlorodimethylvinylsilane to afford the sensitive silyl ether **11** in 93% yield. The silyl ether **11** was then subjected to RCM with catalyst **6** to furnish siloxane **10** in 83% yield. Slow addition of a 0.1 M solution of siloxane **10** in DMF into a solution of APC and TBAF·6H₂O by syringe pump over 48 h furnished macrocycle **9** in a gratifying 74% yield as an oil whose molecular composition was confirmed by high-resolution mass spectrometry. The benzo-fused lactone **9** was formed stereospecifically, as indicated by analysis of its ¹H NMR spectrum. The diagnostic alkene resonance for HC(8) appeared at 6.53 ppm (d, ³J = 15.5 Hz) that correlated well with the coupling constant found for a simpler compound.⁷⁷ The other alkenyl protons HC(9), HC(10), and HC(11) appeared at 6.73 ppm (dd, ³J = 15.5, 9.0 Hz), 6.13 ppm (app t, ³J = 10.0 Hz), and 5.72 ppm (dt, ³J = 10.5, 7.5 Hz), respectively, that also matched well with known analogues.⁷⁷

Discussion

The primary goals of this study were to develop an intramolecular cross-coupling reaction of siloxanes that affords macrolactones in good yields and to prepare a benzo-fused lactone that could serve as the model system for the synthesis of oximidine II. The preparation of macrolactones was enabled by the discovery that fluoride activation of the cross-coupling was effective. The generality of this finding was demonstrated by the synthesis of various macrolactones. The second aim of this study was facilitated by the development of a Mizoroki–Heck reaction of aryl perfluoroalkylsulfonates and a vinylsilane. The elaboration of the Mizoroki–Heck product led to assembly of a benzo-fused macrolactone possessing the core structure of oximidine II.

1. Preparation of Siloxanes 7a–f. The synthesis of the siloxanes used in this study was accomplished in a multistep sequence whereby each reaction step was a modification of a closely related report. The syntheses of siloxanes **7a–f** began from 4-pentyn-1-ol and in a seven-step sequence proceeded uneventfully to yield analytically pure materials in good to excellent yields for all the steps and in all the cases. However, the unexpected sensitivity of the silyl ethers **5a–f** warrants further comment. Initial attempts to purify the silyl ethers by silica gel chromatography led to extensive desilylation and

- (73) (a) Rottlander, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203–208. (b) Lipshutz, B. H.; Buzard, D. J.; Yun, C. S. *Tetrahedron Lett.* **1999**, *40*, 201–204. For reviews of nonafluorobutane sulfonate chemistry, see: (c) Högermeier, J.; Reissig, H. U. *Adv. Synth. Catal.* **2009**, *351*, 2747–2763. (d) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126.
- (74) Fürstner, A.; Nagano, T.; Müller, C.; Seidel, G.; Müller, O. *Chem. Eur. J.* **2007**, *13*, 1452–1462.
- (75) Rehwinkel, H.; Steglich, W. *Synthesis* **1982**, 826–827.
- (76) Otera, J.; Danoh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307–5311.
- (77) For a less functionalized analogue of the same ring system: HC(8), d, *J* = 15.5 Hz; HC(9), dd, *J* = 15.5, 11.1 Hz; HC(10), app t, *J* = 11.1 Hz; HC(11), dt, *J* = 10.6, 4.9 Hz. Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487–3490.

inconsistent results. Although the use of neutral alumina remedied the desilylation problem, the product contained an impurity that led to death of the molybdenum catalyst in the following RCM step. However, adding 1% of Et₃N to the eluting solvent for the silica gel purification eliminated the problem of desilylation. Silyl ethers **5a–f** could be isolated in analytically pure form in excellent yields.

2. Optimization of the Intramolecular Cross-Coupling Reaction. In planning for the key intramolecular macrocyclization reaction of siloxanes **7a–f**, it was expected that only minor adjustments of the conditions developed earlier would be required. Orienting experiments with **7a** quickly revealed the failure of that assumption, but repeating the experiment with rigorous exclusion of oxygen afforded the desired macrocycle **8a** in 46% yield together with the unexpected isomer **8a'** as an inseparable mixture. Isomer **8a'** most likely arose from a rapid, base-catalyzed transactonization after formation of **8a**. This assumption was confirmed by analyzing the reaction every 10 h, which showed that the ratio of **8a:8a'** remained constant. Furthermore, when pure **8a** (obtained from subsequent, selective cyclizations) was exposed to TBAF/THF, within 1 h the ratio of **8a:8a'** was 5.5:1 and after 40 h the ratio was essentially 3:1 (by ¹H NMR analysis). The ratio obtained experimentally (2–3:1) correlates well with molecular modeling calculations that predict a 1.6:1 ratio of **8a:8a'** from the 0.26 kcal/mol difference between **8a** and **8a'**. Thus, to suppress the formation of **8a'** and improve the yield of **8a**, the basicity of TBAF was attenuated. However, conclusive evidence that the fluoride was the culprit could not be inferred since TBAF had been used successfully before with macrolactones.⁷⁸

Landini and Maia found that the basicity and nucleophilicity of the fluoride ion in TBAF could be modulated by adjusting the hydration levels, and this strategy succeeded here as well.^{39,79,80} For example, TBAF·4H₂O or TBAF·6H₂O afforded desired macrolactones **8a** and **8a'** in higher yields (64% and 59%) compared to TBAF·3H₂O. In the more highly hydrated ammonium salts, the fluoride anion forms H-bonds with the water, leading to a decrease in the basicity of TBAF without greatly affecting the nucleophilicity.^{39,81} Thus, at these higher hydration levels the fluoride anion is nucleophilic enough to form the pentacoordinate fluorosilicate intermediate necessary for transmetalation.⁸² The hydrated TBAF·6H₂O was selected over TBAF·4H₂O because at this hydration level the fluoride anion basicity is negligible.³⁹ Investigation of higher hydration levels (TBAF·10H₂O and TBAF·15H₂O) gave lower yields

because at these levels free water is not bound within the TBAF matrix, which affects the nucleophilicity of the fluoride anion.⁸³

Decreasing the loading of TBAF from 10 to 5 equiv increased the yield of lactones **8a** and **8a'**. Although this outcome appears contradictory, it can be understood because the overall reaction concentration has increased. The reaction solvent is a stock solution of 1 M TBAF in THF, so reducing the number of equivalents of TBAF also constitutes a reduction in the reaction volume. The resulting higher concentration of palladium catalyst leads to a faster rate and ultimately a higher yield. Further increasing the concentration of palladium by using 2.5 equiv of TBAF·6H₂O unfortunately led to low yields of isolated macrolactone, presumably because at this loading fluoride activation is not sufficient to promote transmetalation.

3. Survey of Fluoride Promoters for the Intramolecular Cross-Coupling Reaction. A systematic survey of anhydrous and hydrated fluoride promoters revealed that the hydrated fluoride source afforded the highest yields of macrolactones **8a** and **8a'**, while the anhydrous fluoride sources produced the best selectivity. The higher selectivity may be because TBAT and TASF are fluorosilicates and are less basic and nucleophilic compared to TBAF.⁸⁴ The hydrated tetraalkylammonium salts gave variable yields and selectivities that were largely influenced by the structure of the alkyl groups comprising the ammonium salt. For example, TMAF·4H₂O and BTMAF·6H₂O gave similar yields of macrocycle **8a** essentially as a single isomer (Table 3, entries 1–4). The similar reactivity exhibited by these two tetraalkylammonium fluoride ions probably arises from the similarity of their structures and therefore comparable electrostatic interactions of the two fluoride sources. The structure of the tetraalkylammonium salt strongly affects the reactivity of the fluoride ion. Whereas tetramethylammonium is a *T_d* symmetrical ion, tetraethylammonium is found crystallographically in a “Nordic cross” conformation (*S₄*),⁸⁵ and tetrabutylammonium exists in both a flattened cross conformation of *D_{2d}* symmetry and a more tetrahedral-like conformation of *S₄* symmetry.⁸⁶ These structures influence the reactivity of the attendant fluoride ion in two ways, first through the accessibility of the positive charge for Coulombic stabilization⁸⁷ and second through the availability of CH···F[−] hydrogen-bonding interactions.⁸⁸ These two features combine to most effectively attenuate the reactivity of the fluoride ion in the tetramethylammonium salt. With only 4.0 equiv of water, TMAF does not induce the base-promoted isomerization of **8a** to **8a'**, whereas 10.0 equiv of water is required to suppress this isomerization with TBAF (cf. Table 1, entry 10, vs Table 2, entry 1).⁴⁴

The highest yields of the macrolactones **8a** and **8a'** were achieved with TBAF but with variable selectivities. The solvent and the hydration level of the TBAF greatly influenced the outcome. For example, ethereal solvents (THF and dioxane)

- (78) (a) Anquetin, G.; Rawe, S. L.; McMahon, K.; Murphy, E. P.; Murphy, P. V. *Chem. Eur. J.* **2008**, *14*, 1592–1600. (b) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934–3938. (c) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274–9283; *Angew. Chem., Int. Ed.* **2002**, *41*, 4098–4101. (d) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654–5655.
- (79) The structures of hydrated tetraalkylammonium ions have been the subject of careful investigation for many years. A continuum of structures has been identified (depending upon ion structure and hydration level) that ranges from pure anion clathrates through framework structures through hydrogen-bonded networks and finally to discrete polyhedral cluster anions. See: (a) Jeffrey, G. A.; Mak, T. C. *Science* **1965**, *149*, 178–179. (b) McLean, W. J.; Jeffrey, G. A. *J. Chem. Phys.* **1967**, *47*, 414–417. (c) Gennick, I.; Harmon, K. M.; Hartwig, J. *Inorg. Chem.* **1977**, *16*, 2241–2248.
- (80) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452.
- (81) It has been suggested that a stable geometry exists with six water molecules around the fluoride ion of TBAF in an aqueous solution. See: Craig, J. D. C.; Booker, M. H. *J. Solution Chem.* **2000**, *29*, 879.
- (82) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865–4875.

- (83) Rozhkov, I. N.; Kuleshova, N. D. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1976**, *25*, 1919–1923; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, *9*, 2048–2052.
- (84) (a) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901–6905. (b) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167. (c) For an example of reduced TASF basicity over TBAF in a total synthesis, see: Fürstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906–1907.
- (85) Wait, E.; Powell, H. M. *J. Chem. Soc.* **1958**, 1872–1875.
- (86) (a) Snow, M. R.; Ibers, J. A. *Inorg. Chem.* **1973**, *12*, 249–254. (b) Andrenini, B. P.; Dell'Amico, D. B.; Calderazzo, F.; Venturi, M. G. *J. Organomet. Chem.* **1988**, *354*, 369–380, and references cited therein.
- (87) Halpern, M.; Sasson, Y.; Rabinovitz, M. *Tetrahedron* **1982**, *38*, 3183–3187.
- (88) Harmon, K. M.; Gennick, I.; Madeira, S. L. *J. Phys. Chem.* **1974**, *78*, 2585–2591.

afforded lower yields of the macrocycles **8a** and **8a'** compared with the more polar DMF but led to higher selectivity. The higher yield in DMF may be due to increased catalytic efficiency of palladium brought about by weak complexation with DMF.⁶⁵ Another likely contribution by DMF might be its assistance in ionic palladium ligand-exchange reactions.⁸⁹ In silicon-based cross-coupling reactions the critical, anionic hypervalent silicate intermediate needed to effect transmetalation is formed in a preequilibrium step from TBAF. The position of this equilibrium is very likely solvent dependent.^{82,90}

4. Scope of the Intramolecular Cross-Coupling Reaction. The intramolecular cross-coupling reaction displayed good generality for the construction of 11-, 12-, 13-, and 14-membered macrolactones from siloxanes **8a–f**. Comparison of the results shows that even-numbered rings are formed in slightly higher yields compared to the odd-numbered rings (Scheme 4). This trend has been observed previously in the synthesis of macrocycles.¹¹ It is worthy to note that the size of the siloxane ring has a moderate effect on the yields of the macrolactones. For example, in the synthesis of the 12-membered macrolactones, the seven-membered siloxane **7a** afforded **8a** and **8a'** in 78% yield compared to the six-membered siloxane **7b** that gave **8b** in 70% yield. Similarly, in the synthesis of the 13-membered macrolactone, the seven-membered siloxane **7d** afforded **8d** in 61% yield while the six-membered siloxane **7e** furnished **8e** in 53% yield. The seven-membered siloxane has a higher strain compared to the six-membered siloxanes and thus, upon fluoride activation, will undergo a more facile transmetalation compared to the six-membered lactone in order to relieve the strain. The less strained siloxane, on the other hand, may undergo other destructive pathways prior to transmetalation. While this indirect correlation cannot be ascertained with the data at hand, a similar trend was observed in one case in the synthesis of medium-ring cyclic ethers.²²

5. Mizoroki–Heck Reaction of Vinyltrimethylsilane. The Mizoroki–Heck reaction of aryl triflates with vinyltrimethylsilane is challenging because aryl sulfonates possess moderate reactivity.^{73,91} The Heck reaction of aryl triflate **21** under Jeffrey conditions both at ambient temperature and under heating at 80 °C (Table 4, entries 1 and 2) stalled at 43% and 73% conversions, respectively. The inability of the reactions to go to full completion is presumably because oxidative addition could not occur efficiently without ligands.

A survey of ligands known to be useful in Heck reactions identified monodentate phosphines as superior additives. The higher selectivity and yields exhibited by monodentate phosphines compared to bidentate ligands arises because monodentate ligands do not form the unreactive bisphosphine complexes formed by bidentate ligands because of steric crowding.⁶⁵ The success of the bulky monophosphines arises from their ability to effect a fast oxidative addition. In addition, they are able to generate the active T-shaped, three-coordinate palladium complexes.⁷¹ Because of the open coordinate site, these complexes are capable of undergoing facile olefin insertion leading to the Heck product. The polar, aprotic solvents acetonitrile and NMP gave the best results and are known to increase the rate of Heck reactions.^{89,92}

The successful reaction of aryl nonaflate **21** with trimethylvinylsilane under conditions wherein **15** stalled is not unex-

pected because aryl nonaflates display higher reactivity than aryl triflates.⁷³ The enhanced electrophilicity of aryl nonaflates renders them better electrophiles for rapid oxidative addition onto the palladium center and thereupon renders the palladium atom more electrophilic for the carbometalation of the vinylsilane.

6. Synthesis of the Benzo-Fused Lactone 9. The synthesis of **9** followed the established route, except for the opening of lactone **12** with alcohol **13**, by employing the Otera catalyst. **22** was then elaborated in four steps to siloxane **10**. Under the optimized cross-coupling conditions, siloxane **10** furnished the benzo-fused macrocycle (*E,Z*-**9**) in excellent yield (74%) as a single isomer. The yield is comparable to those of the other two 12-membered lactones **8a/8a'** and **8b** that were obtained in 78% and 70% yield, respectively.

The high yield of this silicon-assisted cross-coupling reaction over the Mitsunobu protocol used to synthesize a similar analogue³⁰ can be ascribed to several factors: (1) the added rigidity provided by the benzene ring reduces the entropic penalty of cyclization; (2) the slow addition of the siloxane into the reaction mixture maintains a low concentration of the reactive intermediates to avoid polymerization; and (3) the palladium macrocycle intermediate formed after oxidative addition and transmetalation has reduced strain (compared to the lactonization transition structure) because the two palladium–carbon bonds are longer compared to carbon–carbon bonds. Furthermore, the energetically favored reductive elimination step should overcome the barrier imposed by ring formation more easily than the Mitsunobu reaction that relies on the carboxylate to effect ring closure. This result brings to the fore the power of palladium-catalyzed reactions in facile formation of macrocycles^{21–24,93} that take advantage of reductive elimination as the key step.

Conclusion

The intramolecular cross-coupling reaction of olefinic iodides and cycloalkenylsiloxanes under fluoride activation effectively produced 11-, 12-, 13-, and 14-membered macrolactones containing a conjugated 4,6-*Z,Z*- or 1,3-*E,Z*-diene unit. The fluoride hydration level was critical for controlling the yield and selectivity of macrolactone formation. Key features of this process include (1) high stereospecificity, (2) modular construction of cyclization precursors, (3) flexibility in locating the hydroxyl group at multiple positions in a macrocycle, and (4) generality of ring size. The insights garnered from these studies are being applied in the total syntheses of complex macrocyclic natural products. The results of those studies will be disclosed in due course.

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Supporting Information Available: Detailed experimental procedures, optimization studies, and full characterization of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(89) Spencer, A. J. *Organomet. Chem.* **1983**, 258, 101–108.

(90) Sugiyama, A.; Ohnishi, Y. Y.; Nakaoka, M.; Nakao, Y.; Sato, H.; Sakaki, S.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, 130, 12975–12985.

(91) Ritter, K. *Synthesis* **1993**, 735–762.

(92) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, 108, 3033–3040.

(93) (a) Jägel, J.; Maier, M. E. *Synthesis* **2009**, 2881–2892. (b) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, 124, 5654–5655. (c) Stille, J. K.; Su, H.; Hill, D. H.; Schnelder, P.; Tanaka, M.; Morrison, D. L.; Hegedus, L. S. *Organometallics* **1991**, 10, 1993. (d) Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, 109, 3785–3786.