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Transannular Macrocyclization via Intramolecular *B*-Alkyl Suzuki Reaction

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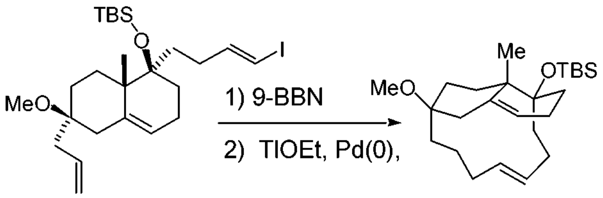
ABSTRACT



Transannular macrocyclizations via intramolecular *B*-alkyl Suzuki reactions are described. Regioselective terminal olefin hydroboration with 9-BBN followed by Pd(0)-catalyzed Suzuki reaction in the presence of a base such as TlOEt at high dilution generates macrocycles with a high degree of control over olefin geometry with isomerically pure *E* or *Z* vinyl iodide substrates. These reactions are complementary to ring closing metathesis (RCM) macrocyclizations and may prove superior in cases where control of olefin geometry is required.

The intermolecular *B*-alkyl Suzuki reaction[1,2] has emerged as a valuable method for the construction of sp^2-sp^3 C−C bonds. Its growing application is evidenced by its use in methodology demonstrations[3] and in natural product syntheses.[4] This reaction played a key role in our total syntheses of epothilones A and B[4e] as well as in 7-epi-Cp-263,114[4f,g] and halichlorine.[4h]

In contrast, the intramolecular variant of the *B*-alkyl Suzuki reaction has not found wide usage. Although the formation of five- and six-membered rings has been reported to occur in a facile manner,[5] the closing of larger ring sizes through intramolecular *B*-alkyl Suzuki reaction has been reported in either very poor yield or not at all.[6] Several years ago we attempted to effect a route to epothilone A via an intramolecular *B*-alkyl Suzuki reaction. However, none of the desired product was obtained.[7] Nonetheless, possible approaches to the total synthesis of several contemporary natural products (including phomactin A,[8,9] Figure 1) occasioned revisitation of such a possibility.

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[4] For use in recent total syntheses, see: (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014. (b) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250. (c) Narukawa, Y.; Nishi, K.; Onoue, H. *Tetrahedron* **1997**, *53*, 539. (d) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818. (e) Balog, A.; Harris, C.; Savin, K.; Zhang, K.-G.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2675. (f) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1485. (g) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197. (h) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (i) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (j) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072.

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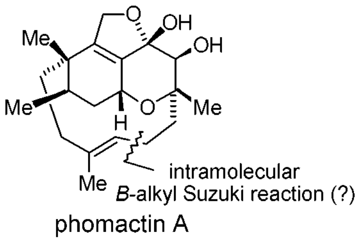
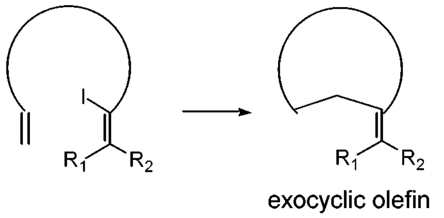
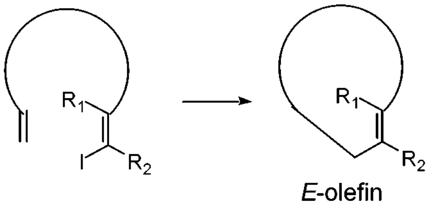


Figure 1.

The most obvious advantage of the intramolecular *B*-alkyl Suzuki reaction over the complementary ring closing metathesis (RCM) reaction is the potentially higher degree of control of olefin geometry of the resulting macrocyclic adduct. Lack of control of olefin geometry is a common problem associated with macrocyclizations via RCM.[10] Conversely, several methods for the stereoselective generation of the vinyl iodides which are relevant to the Suzuki substrates have been reported.[11] Thus, one can imagine the stereospecific formation of exocyclic as well as *E* and *Z* disubstituted, trisubstituted, and even tetrasubstituted olefins contained in macrocycles via this transformation (potential intramolecular *B*-alkyl Suzuki transformations, eqs 1−3).



(1)



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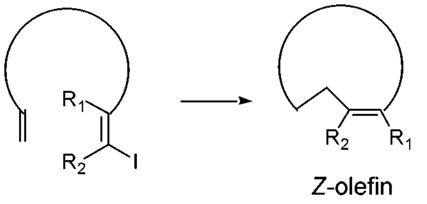
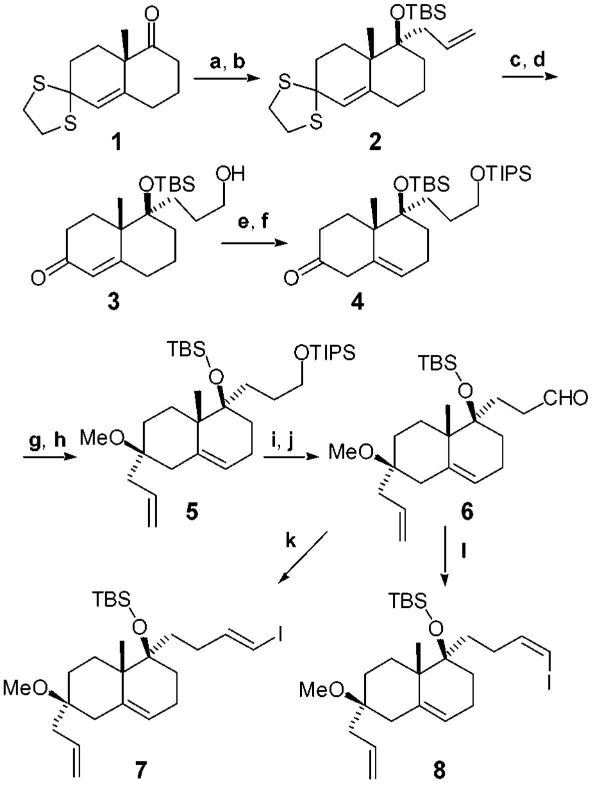


(3)

Our initial objective in this program was to establish the feasibility of the ring-closing *B*-alkyl Suzuki reaction in the context of transannular macrocyclization. Such a capability could serve well in a synthetic venture directed at phomactin A. The *E* and *Z* vinyl iodides **7** and **8**, respectively, were designed to help address the overall feasibility issue. These compounds were synthesized as shown in Scheme 1.

Scheme 1



(**a**) AllMgBr, Et_2O, -78 °C, 92% (dr = 5:1); (**b**) TBSOTf, 2,6-luitidine, CH_2Cl_2, 81%; (**c**) i) 9-BBN, THF, ii) NaOH, H_2O_2, 80%; (**d**) $Tl(NO_3)_3$, MeOH, THF, H_2O, 64%; (**e**) TIPSCl, imidazole, DMF, 99%; (**f**) i) KO*t*-Bu, *t*-BuOH, ii) HOAc, H_2O, 36% (+ 35% s.m.); (**g**) AllMgBr, Et_2O, -78 °C, 82% (dr = 3:1); (**h**) NaH, MeI, THF, reflux, 80%; (**i**) TBAF, DMF, THF, 96%; (**j**) oxalyl chloride, DMSO, CH_2Cl_2, -78 °C, then Et_3N, 23 °C, 76%; (**k**) CHI_3, $CrCl_2$, THF, dioxane, 62% (*E*:*Z* = 11:1); (**l**) ICH_2PPh_3Br, NaHMDS, THF, HMPA, 55% (*Z*:*E* = 13:1).

Ketone **1**[12] was stereoselectively converted to the tertiary silyl ether **2**, which upon hydroboration and removal of the dithiane ketal[12b] yielded **3**. Protection of the primary alcohol followed by deconjugation of the olefin yielded ketone **4**.

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[9] For partial syntheses and syntheses of related structures, see: Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275. (b) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107.

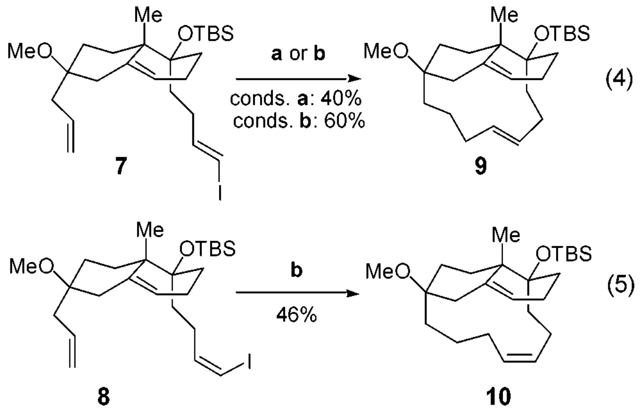
[10] (a) Control of olefin geometry in the RCM reaction has been reported to be problematic in several instances. Several key references are cited by Fürstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234. (b) For an impressive example of attainment of stereoselectivity by RCM, see: Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943.

[11] Methods for *E* vinyl iodide synthesis: (a) Takai, K.; Nitta, K.; Utimo, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. (c) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786. Methods for *Z* vinyl iodide synthesis: (d) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173. (e) Concellon, J. M.; Bernad, P. L.; Perez-Andrez, J. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2384. (f) Corey, E. J.; Cashman, J. R.; Eckrich, T. M.; Corey, D. R. *J. Am. Chem. Soc.* **1985**, *107*, 713. Methods for trisubstituted vinyl iodides: (g) Negishi, E.-i.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501. (h) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.

[12] (a) Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, A.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773. (b) Golinski, M.; Brock, C. P.; Watt, D. S. *J. Org. Chem.* **1993**, *58*, 159.

Stereoselective allylation of **4** and protection of the resulting tertiary alcohol as a methyl ether[13] gave **5**.[14] Silyl ether **5** was converted to aldehyde **6**[15] which in turn was used to provide the *E* and *Z* vinyl iodides **7** and **8** using the methods of Takai[11a,b] and Stork,[11d] respectively.

Gratifyingly, the intramolecular *B*-alkyl Suzuki reaction of vinyl iodide **7** using aqueous $CsCO_3$ as the base afforded macrocycle **9** in 40% yield (eq 4). A dramatic improvement to 60% yield was realized when TlOEt was used as the base.[16] Using the latter conditions, macrocyclization of *Z* vinyl iodide **8** was also effected, forming **10** in 46% yield (eq 5). Not surprisingly, selective hydroboration of the terminal olefin in the presence of the vinyl iodide and trisubstituted olefin moieties of these substrates was realized.[4b,17]

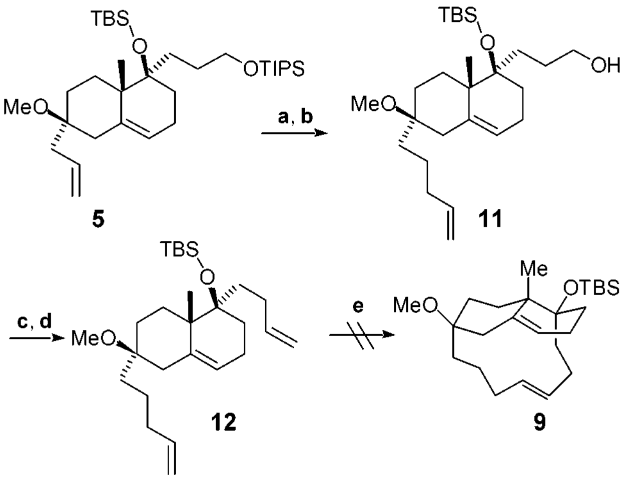


Reaction conds.: (**a**) i) 9-BBN (1.5 equiv), THF (0.5 M), 23 °C; ii) the borane solution was diluted with THF and added via syringe pump to a solution of $Pd(dppf)Cl_2$ (0.2 equiv), $AsPh_3$ (0.2 equiv), $CsCO_3$ (3 equiv) and H_2O (40 equiv) in a 10:1 THF/DMF solution (0.003 M w/r to substrate). (**b**) H_2O (5 equiv) and TlOEt (3 equiv) were added to the borane solution prior to addition to the catalyst solution ($CsCO_3$ and additional H_2O were omitted from these reactions).

We were interested in comparing the efficiency and selectivity (*E* vs *Z*) of the *B*-alkyl Suzuki macrocyclizations of **7** and **8** with the ring-closing metathesis of the corresponding substrate **12** (Scheme 2). The latter was prepared in four steps from intermediate **5**, a common precursor to vinyl iodides **7** and **8**. A conversion of a terminal olefin (cf. **5**) to a two-carbon homologated terminal olefin (cf. **11**) was devised for this purpose. This method involved an apparently unprecedented *B*-alkyl Suzuki hydrovinylation reaction[18] with vinyl bromide with maintenance of double bond integrity.[19]

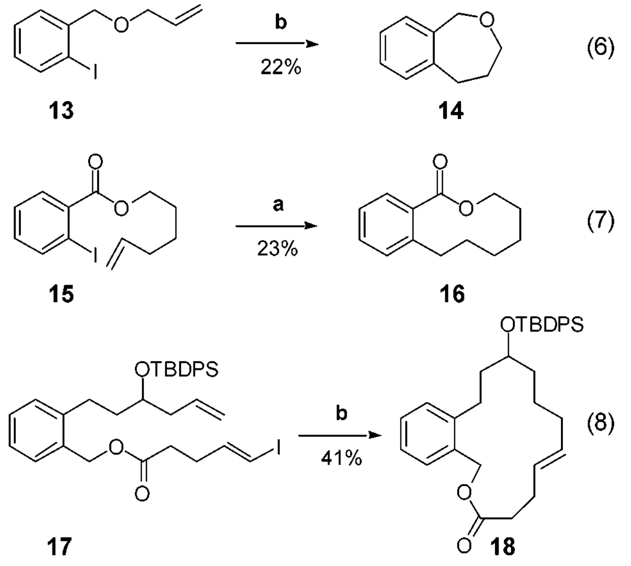
Attempted RCM of substrate **12** with Grubbs' catalyst[20] [$(Cy_3P)_2Cl_2Ru{=}CHPh$] afforded a mixture of dimeric and higher order oligomeric products. Thus, it appears that in this case the intramolecular *B*-alkyl Suzuki macrocyclization is superior to the RCM even at the level of gross feasibility.

Scheme 2



(**a**) i) 9-BBN, THF; ii) H_2O, TlOEt; iii) vinyl bromide, $Pd(dppf)Cl_2$, $AsPh_3$, THF, DMF; (**b**) TBAF, DMF, 65% (2 steps); (**c**) oxalyl chloride, DMSO, CH_2Cl_2, -78 °C, then Et_3N, 23 °C; (**d**) CH_3PPh_3Br, NaHMDS, THF, -78 °C, 64% (2 steps); (**e**) CH_2Cl_2 (0.002 M), reflux, $(Cy_3P)_2Cl_2Ru{=}CHPh$, 48 h.

In a cursory effort to establish the scope and limitations of the intramolecular *B*-alkyl Suzuki reaction, three other substrates were investigated (eqs 6−8). Compounds **13** and **15** bearing *o*-iodo substituents proved to be relatively poor substrates for the cyclization reaction, yielding seven-membered ring **14** (eq 6) and ten-membered ring **16** (eq 7) in 22% and 23% yields, respectively. Increasing the ring size



Reaction conds.: see conditions for equations 4 and 5.

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(16) (a) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691. (b) Humphrey, J. M.; Aggen, J. B.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1996**, *118*, 11759.

(17) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(18) An analogous hydrovinylation using a Negishi-type coupling has been reported by Hoveyda, see ref 10b.

(19) Pd-catalyzed olefin isomerization is a potential problem. See: Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985.

(20) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

and extending the centers of reactivity away from the aromatic ring, as in substrate **17**, led to an improvement of the cyclization efficiency (eq 8). The issues of scope and limitations of our findings will require more study.

In summary, we have demonstrated that the *B*-alkyl Suzuki reaction can be an effective method for transannular macrocyclization. This reaction is complementary to ring-closing metathesis and potentially offers greater control over olefin geometry. We are encouraged by the promising results obtained with **7** and **8**. Application of this methodology to the total synthesis of appropriately challenging target structures is in progress.

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Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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