

Coupling of Alkenes and Alkynes:
Synthesis of the C1–C11 and C18–C28
Fragments of Miyakolide

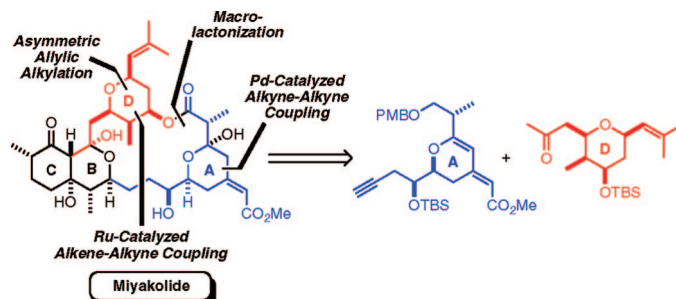
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ABSTRACT



A transition metal-mediated, atom-economical approach toward the crucial A and D rings of miyakolide is described. A Pd-catalyzed alkyne–alkyne coupling/6-*endo-dig* cyclization is employed to assemble the A ring fragment. The key D ring pyran is constructed utilizing an Ru-catalyzed alkene–alkyne coupling followed by a Pd-catalyzed allylic alkylation to establish the all-*cis* stereochemistry.

As part of a program aimed at isolating biologically active natural products from marine sponges, Higa and co-workers in 1992 isolated miyakolide from a sponge of the genus *Polyfibrospongia*.¹ Bioassay results illustrated potent *in vitro* (IC₅₀ 17.1 $\mu\text{g/mL}$ against A-549 human lung carcinoma) and *in vivo* antitumor activity (T/C 123% at 400 $\mu\text{g/Kg}$ against B-16 melanoma).² Aside from its biological activity, miyakolide contains a number of intriguing structural features.^{1,2} Since its isolation, the focus on the pyran A ring has resulted in an elegant anti-aldol approach by Masamune,³ while the first enantioselective total synthesis of *ent*-miyakolide was reported in 1999 by Evans.⁴ Our strategy addresses the synthetic challenges inherent to a macrocyclic of this complexity and illustrates an efficient, convergent route toward **1**.

Immediately, we recognized that the Pd-catalyzed alkyne–alkyne coupling⁵ and Ru-catalyzed alkene–alkyne coupling⁶ strategies developed in our laboratories would be ideally suited for the rapid construction of the A and D rings of miyakolide. Retrosynthetic analysis of **1** involves five key bond disconnections (Scheme 1). First, cleavage of the macrocyclic ester and retro-aldol opening of the trans-fused C and B rings yields intermediate **2**. Trione **2** can further be dissected into fragments **3** and **6** by C11–C12 and C17–C18 cleavage. Alkyne **3** is derived from diyne **4** via a Pd-catalyzed alkyne–alkyne coupling followed by 6-*endo-dig* cyclization, which in turn arises from bis-epoxide **5**.⁷ The backbone of pyran **6** is constructed utilizing the aforementioned Ru-catalyzed alkene–alkyne coupling of epoxide **7** and ether **8**. Subsequent Pd-catalyzed asymmetric allylic alkylation effectively closes the critical D ring. In this manner, the establishment of rings A and D requires

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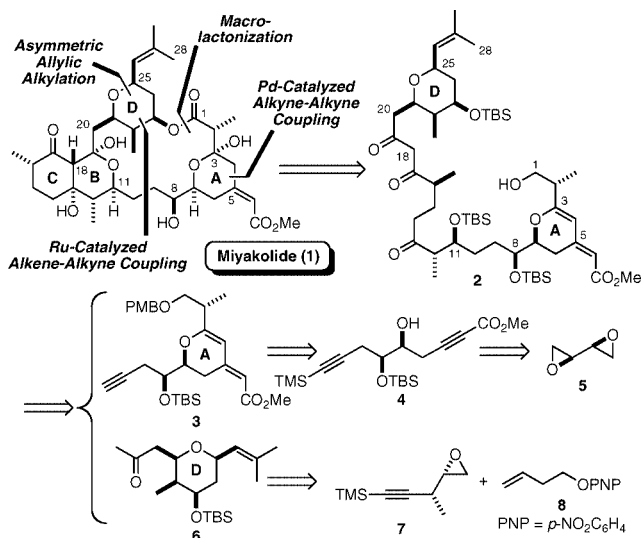
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Scheme 1. Retrosynthesis of Miyakolide (1)

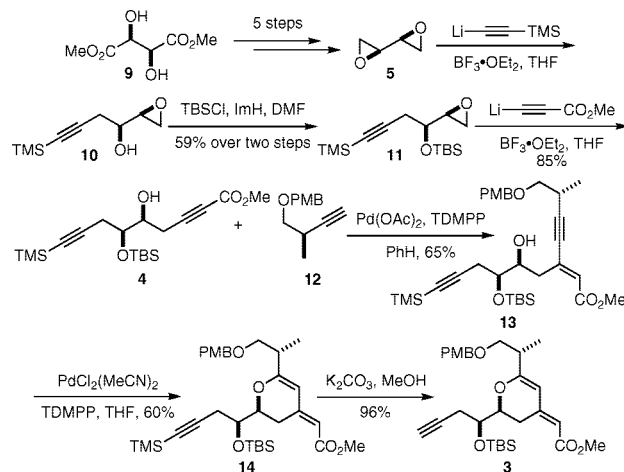


substoichiometric quantities of transition metal catalysts necessary for the stereoselective bond-forming events. Overall, this strategy provides a convergent, atom-economical⁸ approach toward a particularly challenging natural product.

Our synthesis commenced with the assembly of intermediate **3**. The focal point of this sequence is a Pd(II)-catalyzed alkyne–alkyne coupling/cyclization,⁵ which effectively illustrates how our synthesis addresses key structural issues inherent to the A ring of **1**.⁴ In particular, this strategy allows access to either dihydro- or tetrahydropyrans containing an exocyclic α,β -unsaturated ester from a terminal alkyne and suitably functionalized alkynoate. Diyne **4** was synthesized from bisepoxide **5**, which in turn can be obtained in a high-yielding, five-step sequence from L-dimethyl tartrate (**9**) (Scheme 2).⁷ Thus, TMS-acetylide addition to **5** and subsequent protection of the resulting secondary hydroxyl as its TBS ether gave epoxide **11**.⁹ Subsequent addition of methyl propiolate provided the stereochemically pure diyne **4**.

With diyne **4** in hand, our attention turned toward the crucial alkyne–alkyne cross-coupling with alkyne **12**. Previous reports indicated that the desired glucal could be obtained directly in a one-pot procedure by treating alkynoate **4** and alkyne **12** with Pd(OAc)₂ in the presence of tris(2,6-dimethoxyphenyl)phosphine (TDMPP).⁵ Unfortunately, this reaction proved to be low yielding and lacked reproducibility. However, in studies directed toward the synthesis of bryostatin **7**, we found that by employing PdCl₂(MeCN)₂ in the 6-*endo-dig* cyclization, the ratio of undesired side products could be suppressed.¹⁰ Thus, treatment of **4** and alkyne **12** with Pd(OAc)₂ (10 mol %) and TDMPP (5 mol %) afforded

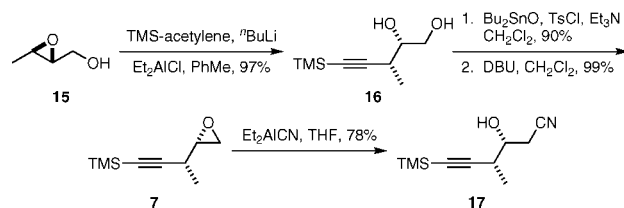
Scheme 2. Construction of the A Ring Fragment **3**



the cross-coupled product **13** in 65% yield. Subsequent treatment of enoate **13** with PdCl₂(MeCN)₂ (10 mol %) and TDMPP (6 mol %) provided the desired cyclization product **14** in a satisfactory yield of 60%. Finally, deprotection of the alkyne moiety in **14** yielded fragment **3**. We found that if enyne **13** was isolated, and the oxy-palladation cyclization performed in a discrete second step, the overall yield of the process was improved. Thus, by isolating intermediate **13**, clean glucal **14** could be produced in a matter of 14–16 h in 40% overall yield, a protocol that was used for subsequent scale-up efforts.

The ruthenium-catalyzed alkene–alkyne cross-coupling, in which the 1,4-diene product may be subjected to palladium-catalyzed allylic substitution without isolation, has proven to be a valuable tool in accessing heterocycles of various ring sizes stereoselectively.^{6,11} We envisioned that such a sequence would constitute an efficient method to assemble the carbon framework of the D ring pyran fragment **6**. Initially, we targeted alkyne **17**, containing a β -cyano alcohol functional moiety, as the alkyne substrate (Scheme 3). A regioselective addition of TMS-acetylide to epoxide

Scheme 3. Synthesis of Alkyne **17**



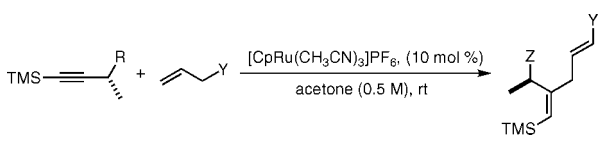
15,^{12,13} chemoselective tosylation of the resulting diol **16** with Bu₂SnO (10 mol %)¹⁴ followed by treatment with DBU

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Table 1. Ruthenium-Catalyzed Alkene–Alkyne Coupling^a


entry	R	Y	Z	yield ^b
1				NR
2				NR
3				57%
4				93%
5				10%
6				13%
7				42%
8				81% ^c

^a Conditions: all reactions were performed with 1 equiv of alkyne and 1 equiv of alkene. ^b Only the branched 1,4-diene products were obtained. ^c 93% yield based on recovered starting material.

provided epoxide **7** (89% overall yield). At this stage, treatment of **7** with Et₂AlCN gave nitrile **17** as a latent acetyl group to be unmasked at a later stage. In an effort to directly install the trisubstituted olefin in **6**, ether **20** was chosen as the alkene component in the coupling reaction (Table 1, entry 1). Unfortunately, a mixture of nitrile **17**, alkene **20** and [CpRu(MeCN)₃]PF₆ (10 mol %) returned a near quantitative yield of both substrates. Thus, we embarked on an examination of alternative alkene–alkyne coupling substrates.

To determine if the nitrile group was somehow hindering the reaction, selective monosilylation of diol **16** yielded alkyne **18**. Subsequent treatment with **20** in the presence of [CpRu(MeCN)₃]PF₆ failed to provide the desired product (entry 2). At this stage, we explored the use of the

β,γ-unsaturated ester **21**, a substrate that was shown to be quite viable toward the synthesis of bryostatin **7**. Thus, treatment of alkynes **17** and **18** with **21** separately under the aforementioned conditions, afforded dienes **22c** and **22d**, in 57% and 93% yield, respectively (entries 3 and 4). Surprisingly, concomitant TBS deprotection and acetonide formation occurred upon alkene–alkyne coupling of **18**. Unfortunately, pyran formation via a subsequent Michael addition to α,β-unsaturated ester **22d** proved ineffectual. However, the in situ desilylation–acetonide formation was a pleasant observation as one can certainly imagine a sequence wherein a protecting group exchange and carbon–carbon bond formation, performed in a *three step, one-pot* tandem operation, would be synthetically practical.

Nevertheless, we explored the possibility of installing the isopropylidene moiety at a later stage via olefin cross-metathesis.¹⁵ To that end, ether **8** was examined, but failed to provide the corresponding 1,4-dienes in acceptable yield from reaction with alkynes **17** and **19** (entries 5 and 6). Given the low catalyst turnover in the presence of the metal coordinating nitrile and PMB group we next examined diol **16**. Treatment with ether **8** did provide 1,4-diene **22g** in which in situ acetonide protection occurred, but in poor yield (entry 7). However, treatment of epoxide **7** and aryl ether **8** with [CpRu(MeCN)₃]PF₆ gave the desired diene **22h** in a gratifying 81% yield (entry 8). It should be noted that although the reaction conditions are Lewis acidic enough to facilitate desilylation and ketalization with acetone, the epoxide moiety in **7** remained intact. However, if the acetone was not freshly distilled just prior to use we observed formation of acetonide **22g**. The synthesis of **22h** proved quite reliable, even on multigram scale, and was subsequently employed in the synthesis of pyran **6**.

Two distinct observations upon an examination of the results depicted in Table 1 deserve comment. First, only the so-called branched isomer is obtained from the productive alkene–alkyne couplings. This predominant regioselectivity has previously been observed with TMS-protected alkynes.^{11b} Second, ester **21** proved to be a better alkene substrate than ethers **20** and **8** as indicated by entries 2–5 and 7. Both observations lend insight into the overall process. As illustrated in Scheme 4, upon formation of intermediate **A** by coordination of the alkene and alkyne in a head-to-tail arrangement, oxidative addition yields ruthenacycle **B**. At this stage, β-hydride elimination gives **C** followed by reductive elimination, to the branched 1,4-diene. Our results seem to indicate that conversion from **B** to **C** is the product-determining step of the catalytic cycle. This would explain why ester **21** is a better alkene substrate as it would activate the α-hydrogen (in red) for elimination better than ether **8**. The selectivity for the branched isomer indicates that formation of ruthenacycle **B** is preferred, presumably for steric effects, wherein C–C bond formation preferentially occurs at the less hindered alkyne carbon.¹⁶ Thus, β-hydride

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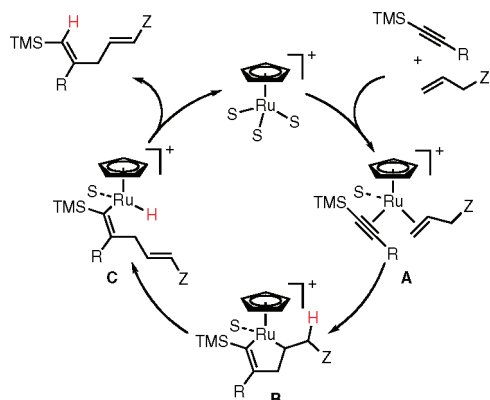
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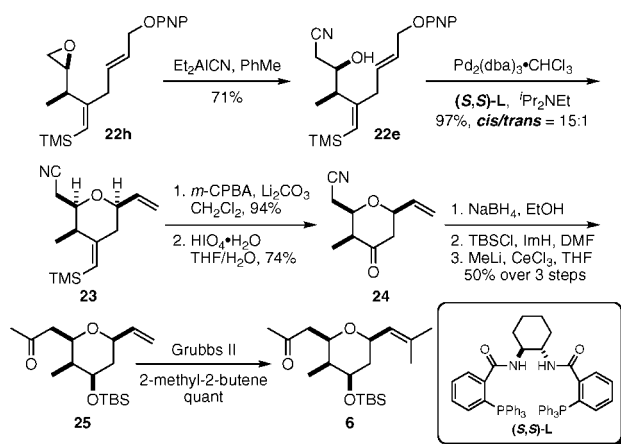
Scheme 4. Proposed Mechanism of the Alkene–Alkyne Coupling



elimination occurs at a faster rate, thereby leading to the observed product distribution.

With a practical route toward diene **22h** in hand, our pursuit of pyran **6** continued with an addition of Et_2AlCN to epoxide **22h** to yield the allylic alkylation precursor **22e** (Scheme 5).¹⁷ Treatment of allyl ether **22e** with $\text{Pd}_2(\text{dba})_3$

Scheme 5. Final Assembly of Pyran **6**



CHCl_3 (2 mol %) in the presence of $(S,S)\text{-L}$ and Hunig's base effectively closed the pyran ring with excellent diastereoselectivity (15:1) favoring *cis* isomer **23** in a catalyst

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controlled rather than substrate controlled reaction.⁵ It should be noted that employing $[\text{Pd}(\eta\text{-C}^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ as the catalyst or switching to DBU as the base resulted in poor *cis/trans* selectivity. This would imply that as the rate of the cyclization was increased, a substantial amount of substrate **22e** underwent allylic alkylation unchecked by the presence of ligand $(S,S)\text{-L}$.

The final assembly of pyran **6** involved chemoselective epoxidation of the vinylsilane in pyran **23**¹⁸ and subsequent cleavage with periodic acid yielding pyranone **24**.¹⁹ Reduction with NaBH_4 , TBS protection, and subsequent methylcerium addition to the nitrile moiety gave ketone **25**.²⁰ Isopropylidene installation via olefin cross-metathesis in the presence of Grubbs' second-generation catalyst yielded pyran **6** in quantitative yield.²¹ This route effectively completes the A ring fragment en route toward the title compound, miyakolide.

In summary, an efficient, convergent approach toward miyakolide has been examined. Through the use of atom-economical transformations, the rapid assembly of advanced intermediates with high levels of enantio- and diastereocontrol are discussed. The use of transition metal-mediated addition reactions to provide more structurally complex intermediates is just one of the highlights in the synthetic design. Examination of the ruthenium-catalyzed alkene–alkyne coupling highlight some important aspects of the transformation, in particular, the ability to exploit the latent Lewis acidity of the catalyst to initiate in situ deprotection–protection sequences, as well as lending insight into the catalytic process.

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Supporting Information Available: Experimental procedures and copies of ^1H NMR spectra are provided for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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