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

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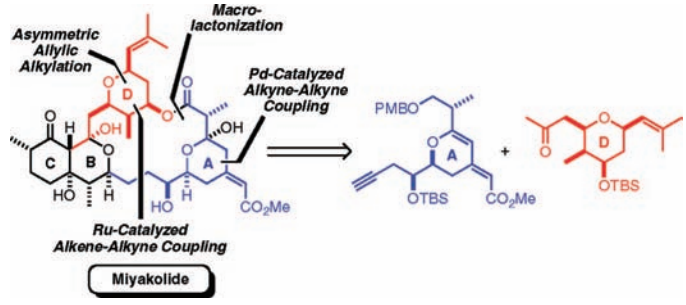
ABSTRACT



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 (IC_{50} 17.1 μg/mL against A-549 human lung carcinoma) and in vivo antitumor activity (T/C 123% at 400 μg/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 macrolide of this complexity and illustrates an efficient, convergent route toward **1**.

Immediately, we recognized that the Pd-catalyzed alkyne−alkyne coupling[5] and Ru-catalyzed alkene−alkyne coupling[6] strategies developed in our laboratories would be idealy 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 macrolide 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

(1) Higa, T.; Tanaka, J.; Komesu, M. *J. Am. Chem. Soc.* **1992**, *114*, 7587.
(2) (a) Pettit, G. *J. Nat. Prod.* **1996**, *59*, 812. (b) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841.
(3) Takehiko, Y.; Song, J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978.
(4) Evans, D.; Ripin, D.; Halstead, D.; Campos, K. *J. Am. Chem. Soc.* **1999**, *121*, 6816.
(5) Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 11727.
(6) Trost, B. M.; Machacek, M. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4693.
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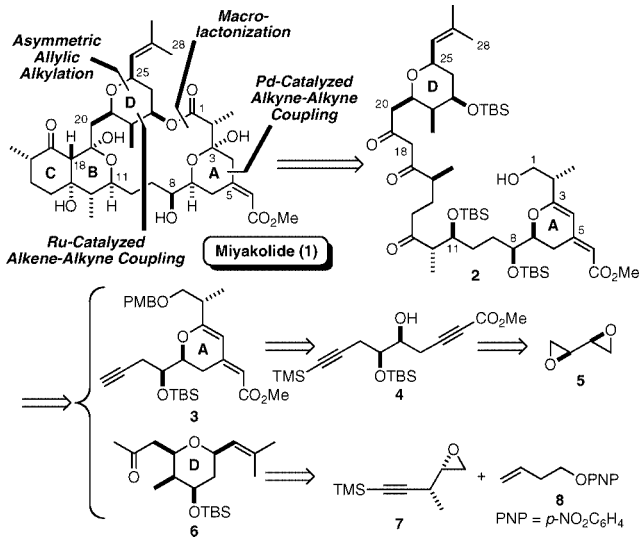
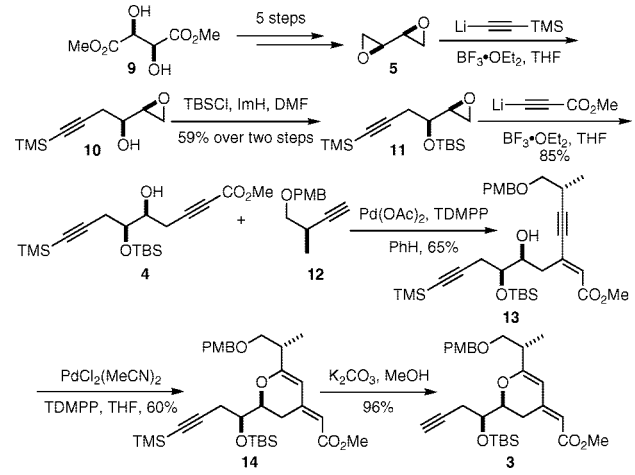
Scheme 1. Retrosynthesis of Miyakolide (**1**)



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



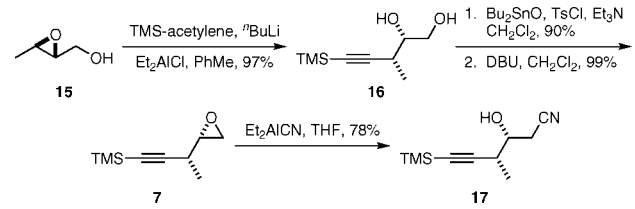
substoichiometric quanitites of transition metal catalysts necessary for the stereoselective bond-forming events. Overall, this strategy provides a convergent, atom-economical[8] approach toward a particularly challenging natural product.

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 $PdCl_2(MeCN)_2$ 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 the cross-coupled product **13** in 65% yield. Subsequent treatment of enoate **13** with $PdCl_2(MeCN)_2$ (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

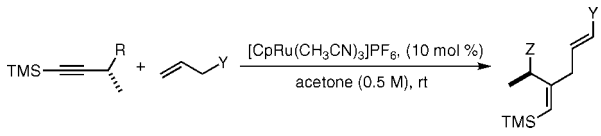
Scheme 3. Synthesis of Alkyne **17**

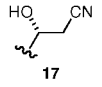
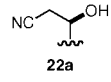
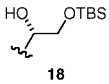
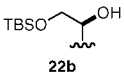
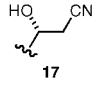
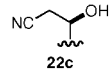
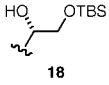
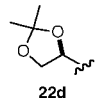
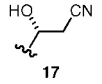
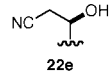
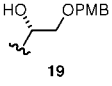
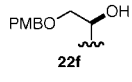
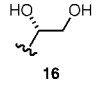
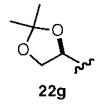


15,[12,13] chemoselective tosylation of the resulting diol **16** with Bu_2SnO (10 mol %)[14] followed by treatment with DBU

(8) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
(9) Boeckman, R. K.; Liu, X. *Synthesis* **2002**, 2138.
(10) Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007**, *129*, 2206.
(11) (a) Trost, B. M.; Indolese, A. F.; Mueller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. (b) Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. *Org. Lett.* **2000**, *2*, 1761.

Table 1. Ruthenium-Catalyzed Alkene−Alkyne Coupling[a]



entry	R	Y	Z	yield[b]
1	 **17**	$C(Me)_2OPNP$ **20**	 **22a**	NR
2	 **18**	$C(Me)_2OPNP$ **20**	 **22b**	NR
3	 **17**	CO_2Me **21**	 **22c**	57%
4	 **18**	CO_2Me **21**	 **22d**	***93%***
5	 **17**	CH_2OPNP **8**	 **22e**	10%
6	 **19**	CH_2OPNP **8**	 **22f**	13%
7	 **16**	CH_2OPNP **8**	 **22g**	42%
8	 **7**	CH_2OPNP **8**	 **22h**	***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 Et_2AlCN 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 $[CpRu(MeCN)_3]PF_6$ (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 $[CpRu(MeCN)_3]PF_6$ 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). Suprisingly, 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 $[CpRu(MeCN)_3]PF_6$ 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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(13) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.
(14) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578.
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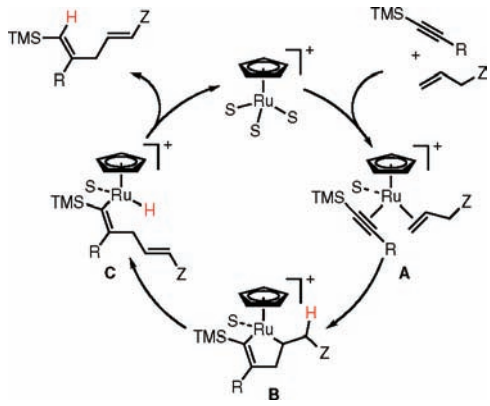
(16) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991.

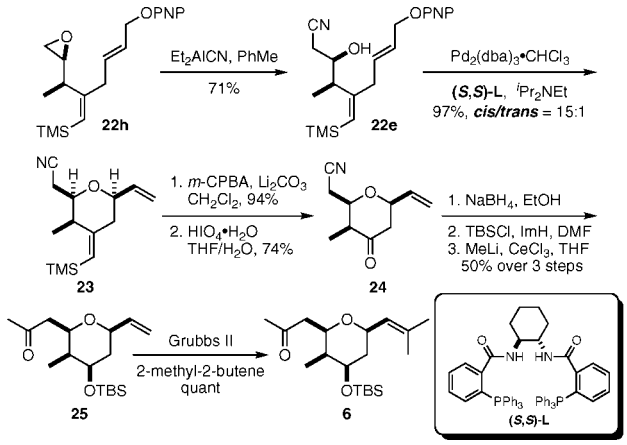
Scheme 4. Proposed Mechanism of the Alkene−Alkyne Coupling



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 $Pd_2(dba)_3$•$CHCl_3$ (2 mol %) in the presence of (*S*,*S*)-**L** and Hunig's base effectively closed the pyran ring with excellent diastereoselectivity (15:1) favoring cis isomer **23** in a catalyst controlled rather than substrate controlled reaction.[5] It should be noted that employing $[Pd(\eta\text{-}C^3\text{-}C_3H_5)Cl]_2$ 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*)-**L**.

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



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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