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A Ru-Catalyzed Tandem Alkyne–Enone Coupling/Michael Addition: Synthesis of 4-Methylene-2,6-*cis*-tetrahydropyrans

Barry M. Trost,* Hanbiao Yang, and Georg Wuitschik

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@stanford.edu

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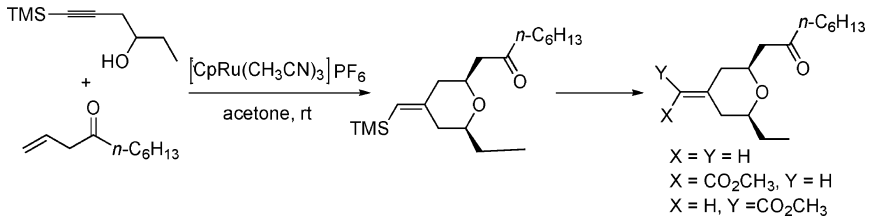
ABSTRACT



A Ru-catalyzed tandem alkyne–enone coupling/Michael addition reaction is reported. It provides an efficient, atom-economic entry to 4-methylene-2,6-*cis*-tetrahydropyrans from simple, readily available homopropargylic alcohols and *β*,*γ*-unsaturated enones in good yields. Further functionalization of the resultant vinylsilane leads to the synthesis of either geometrically defined trisubstituted alkene exocyclic to the 2,6-*cis*-dihydropyran.

Natural products provide constant challenges and inspiration for synthetic chemists. The tetrahydropyran ring system is present in a range of natural products as illustrated in the case of the bryostatins, a family of marine natural products isolated from the bryozoan invertebrates *Bulgula neritina* and *Amathia convulata*. They have attracted a great deal of attention from the synthetic community owing to their diverse biological activities and novel structural motif.[1] While several elegant total syntheses exist, the potential utility of this family of compounds encourages the development of more concise strategies.[2−4] Among the challenges presented by the bryostatins, control of the alkene geometry exocyclic to the tetrahydropyran rings (ring B and ring C) represents a formidable task.[3−6]

Cycloaddition-type reactions enhance synthetic efficiency by creating molecular complexity in a single event with a high atom economy.[7] As part of our ongoing effort to effect a more efficient synthesis of bryostatin natural products, we became intrigued by a proposal of forming 4-methylene-2,6-*cis*-tetrahydropyrans in an annulation process as illustrated in Scheme 1.[8,9]

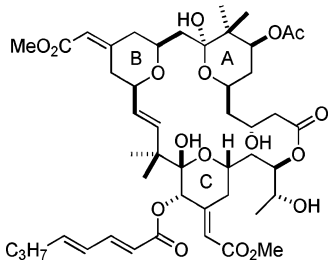


Figure 1. Bryostatin 1.

(1) (a) Bryostatin 1 isolation and structure determination: Pettit, G. R.; Herald, C. L.; Clardy, J.; Arnold E.; Doubek, D. L.; Herald, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 8648. (b) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841. (c) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigero, M. *Nat. Prod. Rep*. **2002**, *19*, 413.

(2) (a) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587. (b) Kageyama, M.; Tamaru, T.; Nantz, M. H.; Roberts, J. C.; Somfrai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407.

(3) (a) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2354. (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540.

(4) Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290.

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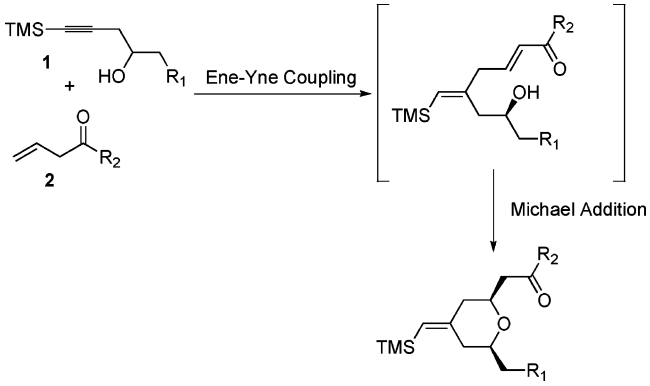
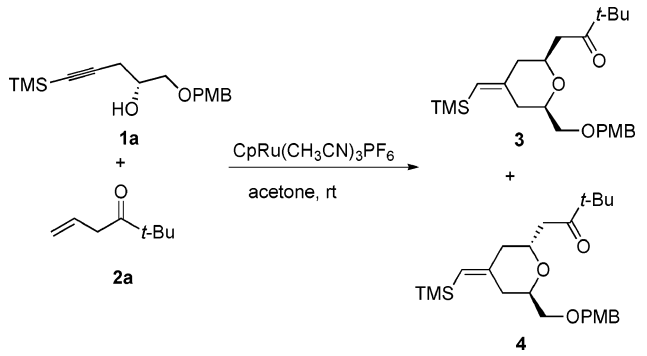
Scheme 1. Proposed Tetrahydropyran Synthesis



To test the viability of the concept, 1-(4-methoxybenzyloxy)-5-trimethylsilanylpent-4-ol **1a** and 2,2-dimethylhex-5-en-3-one **2a** were treated with $[CpRu(CH_3CN)_3]PF_6$[10] in acetone (Scheme 2). Gratifyingly, the reaction went smoothly

Scheme 2. A Model Study



and provided the 2,6-*cis*-tetrahydropyran **3**[11] and **4** as the major product (Table 1, entry 1) without any detectable amount of the hydroxyenone intermediate (Scheme 1).

Efforts to optimize the reaction are summarized in Table 1. It was found that the best solvent for the reaction is acetone

Table 1. Optimization of Alkyne−Enone Coupling[a]

entry	solvent	connc (M)	cat. loading (mol %)	**2/1** ratio	yield[b] cis(trans)
1	acetone	0.1	10	1	31%
2	acetone	0.1	10	1.8	43% (6%)
3	acetone	0.1	30	1	36%
4	acetone	0.4	10	1.2	41% (6%)
5	acetone/H_2O (9/1)	0.4	10	3	trace
6	acetone/DMF (9/1)	0.4	10	3	mostly starting material
7	2-butanone	0.4	10	3	63% (13%)
8	acetone	0.4	10	3	68% (15%)

[a] Reaction performed at room temperature with $[CpRu(CH_3CN)_3]PF_6$ for 20 h. [b] Isolated yields of cis-isomer and trans-isomers (in parentheses) after column chromatography.

as the addition of water and DMF inhibited the reaction (entries 5 and 6), while 2-butanone gave a slightly lower yield (entry 7). Higher concentration led to better conversion as expected from a typical bimolecular reaction (entry 4). However, higher catalyst loading did not lead to a substantially higher yield (entry 3). To achieve both reasonable conversion and yield, excess enone was employed. The best yield was achieved with acetone as solvent, 0.4 M concentration of alkyne, and 3 equiv of enone (entry 8).

To further probe the scope and limitations of this reaction, a variety of propargylic alcohols and β,γ-unsaturated enones[12] were prepared and subjected to the optimized conditions. The results are summarized in Table 2. A variety of groups, including TBDPS, benzyl, *p*-methoxybenzyl, acetyl, and the hindered TBS, were tolerated. Since excess enone is necessary to achieve good conversion and yield, the ability to recover the unreacted enone after the reaction is desirable, especially when it is precious. To our delight, enones with *tert*-alkyl groups can be mostly recovered (entries 7, 8, and 10), which bodes well for the byrostatin synthesis. On the other hand, when dec-1-en-4-one **2b** was used, it was recovered together with 15−20% of the isomerized α,β-enone. The reaction tolerated branching at the propargylic position, albeit with a slightly lower yield (entry 6). Interestingly, complete chemoselectivity was observed for two different types of alkenes (entry 10). No product derived from the coupling of the alkene bearing an allylic oxygen with an alkyne was detected. The cis/trans ratios ranged from 5/1 to 8/1.[13]

Preliminary studies suggest the cis/trans-isomers are not equilibrating under the reaction conditions.[14] The preference

(5) A tandem palladium-catalyzed alkyne/alkynoate coupling has been used to synthesize dihydropyrans with geometrically defined exocyclic alkyl enoates, see: Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 11727.

(6) (a) Trost, B. M.; Machachek, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693. (b) Hanson, E. C.; Lee, D. *Tetrahedron Lett.* **2004**, *45*, 7151.

(7) (a) Wender, P. A.; Miller, B. L. *Organic Synthesis*: *Theory and Application*; Hudlicky, T., Ed.; JAI: Greenwich, 1993; Vol. 2, p 70. (b) Bertz, S. H. *New J. Chem.* **2003**, *27*, 860.

(8) (a) For an application of Ru-catalyzed alkyne/β,δ-unsaturated ester coupling in synthesis, see: Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc*. **2004**, *126*, 48. (b) For a pyran annulation reaction, see: Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189.

(9) Michael addition has been used to assembly the B-ring of bryostatins, see: (a) Ball, M.; Baron, A.; Bradshaw, B.; Omori, H.; MacCormick, S.; Thomas, E. J. *Tetrahedron Lett.* **2004**, *45*, 8737. (b) O'Brien, M.; Taylor, N. H.; Thomas, E. J. *Tetrahedron Lett.* **2002**, *43*, 5491. (c) Yadav, J. S.; Bandyopadhyay, A.; Kunwar, A. C. *Tetrahedron Lett.* **2002**, *43*, 5491.

(10) (a) Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485. (b) Trost, B. M.; Older, C. M. *Organometallics* **2002**, *21*, 2544. (c) Kundig, E. P.; Monnier, F. R. *Adv. Synth. Catal.* **2004**, *346*, 901.

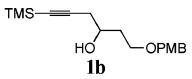
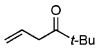
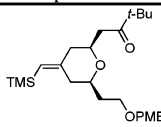
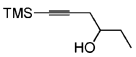
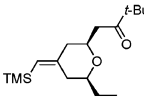
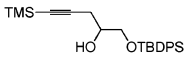
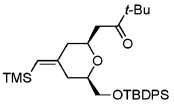
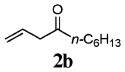
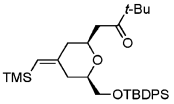
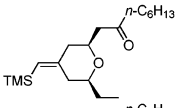
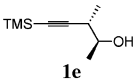
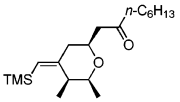
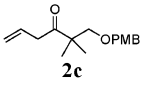
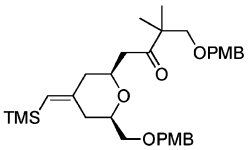
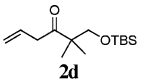
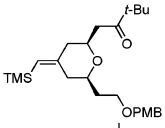
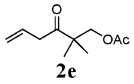
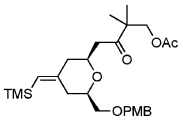
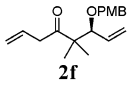
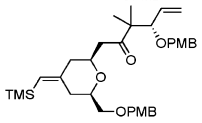
(11) The cis-configuration was established by NOE studies.

(12) Le Roux, C.; Dubac, J. *Organometallics* **1996**, *15*, 4646.

(13) The trans-isomers were not obtained pure after column chromatography except entry 10. The ratios were determined by integrating two different vinyl protons, which are usually separated by 0.03 PPM in the 5.20−5.30 region.

(14) Efforts trying to equilibrate the cis/trans-isomers under either basic (NaOMe, LiOMe, $Mg(OCH)_2$) or acidic (Amberlyst 15) conditions led to decomposition. Resubjecting the trans-isomer of **5** to the reaction conditions did not give any **5**. However, similar diastereoselectivity was claimed to be obtained under thermodynamically controlled conditions (ref 9b).

Table 2. Representative Examples of Tandem Alkyne−Enone Coupling/Michael Addition Reaction[a]

entry	alkyne	enone	product	yield[b]
1	 **1b**	 **2a**		58%
2	 **1c**	**2a**		80%
3	 **1d**	**2a**		56%
4	**1b**	 **2b**		64%
5	**1c**	**2b**		62%
6	 **1e**	**2b**		54%
7	**1a**	 **2c**		69%
8	**1a**	 **2d**		58%
9	**1a**	 **2e**		77%
10	**1a**	 **2f**		39%

[a] Reactions performed at 0.5 M alkyne concentration with 3 equiv of enone and 10 mol % of $[CpRu(CH_3CN)_3]PF_6$ in acetone at room temperature for 40 h. [b] Isolated yield of pure cis-isomer.

for formation of the cis product implicates a late transition state for the cyclization wherein relative product stability will play a more significant role. The variation in diastereoselectivity for similar structures presumably arises as a reflection of the relative importance of product stability in the transition state of each cyclization. Attempts to establish the thermodynamic ratio were thwarted by acid- and base-catalyzed decomposition.[14]

The resultant geometrically defined exocyclic vinylsilane provides a handle for further functionalization (Scheme 3). Protodesilylation[6a] of **5** went smoothly to give **6** without double bond migration. Vinyl iodide formation[6a] also proceeded efficiently and the product was subsequently carbonylated[15] to give methyl enoate **7**. Furthermore, we were able to invert the double bond geometry through an epoxidation, bromohydrin formation, and siloxy elimination sequence[16] to give the inverted bromide **8**, which was also carbonylated[17] with high efficiency. Thus, from one geometrically defined vinylsilane either geometric isomer of the exocyclic enoate is cleanly available.

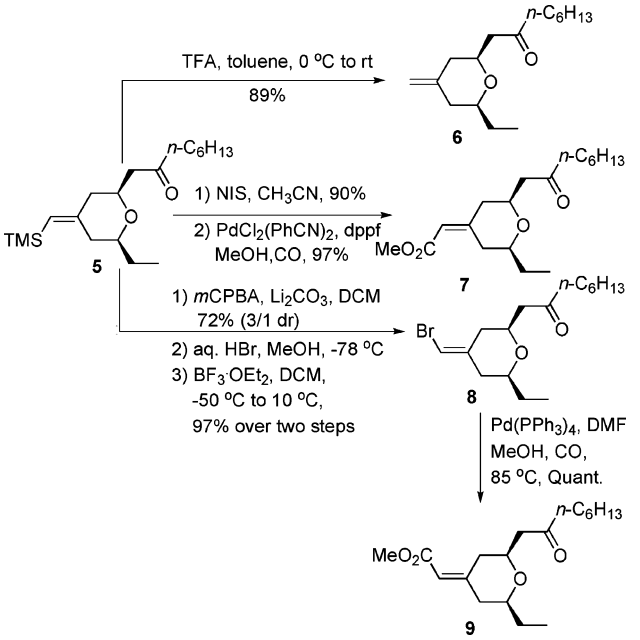
In summary, a Ru-catalyzed tandem alkyne−enone coupling/Michael addition reaction is reported. In no case has the presumed enone intermediate been observed. Since uncatalyzed additions of alcohols to enones are not antici-

(15) Beller, M.; Magnerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, 1098.

(16) Chou, S. S. P.; Kuo, H. L.; Wang, C. J.; Tsai, C. Y.; Sun, C. M. *J. Org. Chem.* **1989**, *54*, 868.

(17) (a) Qing, F. L.; Yue, X. J. *Tetrahedron Lett.* **1997**, *38*, 8067. (b) Cacchi, S.; Morea, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*. 1109.

Scheme 3. Transformations of the Vinylsilane



pated to be fast,[9a] it is likely that the Ru complex also catalyzes this step. It provides an efficient, atom-economic entry to 4-methylene-2,6-*cis*-tetrahydropyrans from simple, readily available homopropargylic alcohols and β,γ-unsaturated enones in good yield. The resultant vinylsilane provides a handle for further fuctionalization, allowing protodesilylation and the synthesis of vinyl halides with either olefin geometry. Subsequent metal-catalyzed cross-coupling reactions lead to the synthesis of either geometrically defined trisubstituted alkene exocyclic to the 2,6-*cis*-dihydropyran, which are difficult to access through other synthetic means. In addition, oxidative cleavage of the exocyclic double bonds also provides access to 4-tetrahydropyranones and their alcohol analogues.

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Supporting Information Available: Experimental procedures for the preparation of new compounds as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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