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Palladium-Induced Cyclizations for the Synthesis of *cis*-2,5-Disubstituted-3-methylenetetrahydrofurans: Studies of the C_7−C_{22} Core of Amphidinolide K

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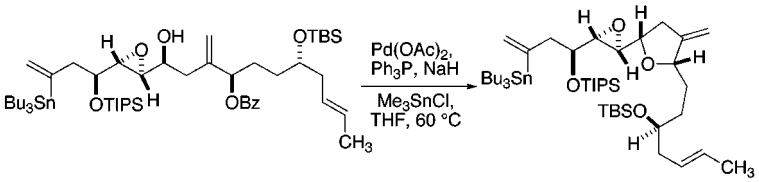
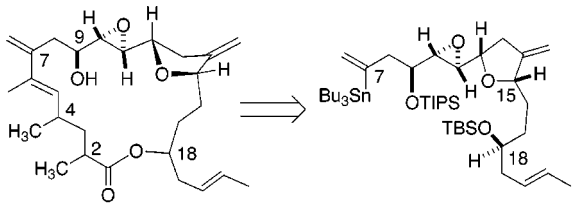
ABSTRACT



The diastereoselective synthesis of *cis*-2,5-disubstituted-3-methylenetetrahydrofurans via Pd(0)-catalyzed cyclization of 2-methylene-1,4-diols is described. Investigations into the scope of the reaction and its application toward the synthesis of amphidinolide K is reported.

For nearly two decades, there has been continuing interest in methods leading to the stereocontrolled preparation of highly substituted tetrahydrofurans.[1,2] These advances were inspired, in large measure, by the prevalence of the THF ring system within polyether antibiotics and marine natural products.[3] As part of our longstanding interest in the synthesis of these important oxacycles,[4] our recent efforts for the synthesis of the C_7−C_{22} domain of amphidinolide K (**1**) required the preparation of 2,5-*cis*-substituted tetrahydrofuran **2**.[5] In this Letter, we report our investigations of palladium-catalyzed cyclizations of 2-methylene-1,4-diol monobenzoates as a general method for the diastereoselective synthesis of *cis*-2,5-disubstituted-3-methylenetetrahydrofurans.



1 (Amphidinolide K) **2**

In 1983, Stork and Poirier described effective chirality transfer in the palladium-assisted S_N' cyclization of γ-hydroxy allylic esters for the synthesis of optically active tetrahydrofurans.[6] Pioneering work of Trost established the regioselectivity for internal O-capture of π-allyl palladium complexes in the reactions of substituted trimethylenemethane (TMM) palladium complexes.[7] The formation of 3-methylenetetrahydrofurans **3** and **4** occurs via aldehyde

(1) (a) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (b) Williams, D. R.; Phillips, J. G.; Barner, B. A. *J. Am. Chem. Soc.* **1981**, *103*, 7398. For recent examples, see: (c) Petasis, N. A.; Lu, S.-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394. (d) Beauchamp, T. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1995**, *117*, 12873. (e) Li, P.; Wang, T.; Emge, T.; Zhao, K. *J. Am. Chem. Soc.* **1998**, *120*, 7391.

(2) For a recent review, see: Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1771.

(3) (a) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792. (b) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971. (c) MacMillan, D. W.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

(4) (a) Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067. (b) Williams, D. R.; Phillips, J. G. *Tetrahedron* **1986**, *42*, 3013. (c) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641.

(5) Ishibashi, M.; Sato, M.; Kobayashi, J. *J. Org. Chem.* **1993**, *58*, 6928.

(6) Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073.

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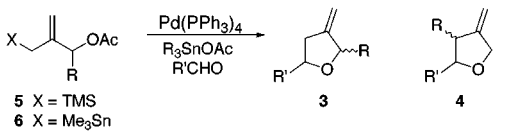
cycloaddition with allylsilane precursor **5** via the initial generation of kinetic and thermodynamic TMM complexes. Generally the corresponding allylstannanes **6** were not as versatile in these reactions and failed in cases of saturated aldehydes.



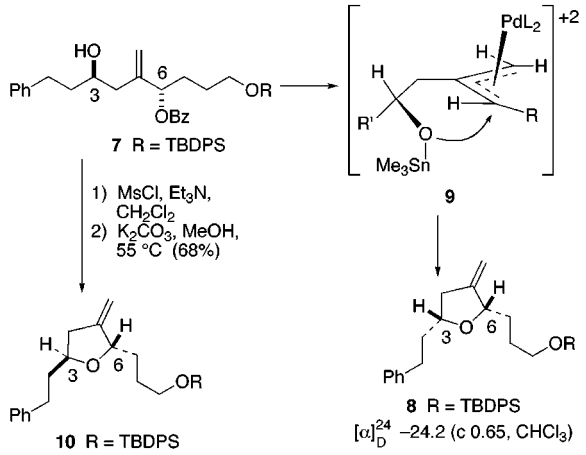
5 X = TMS
6 X = Me_3Sn

3 **4**

We have deployed a stepwise variant of this reaction to address our concerns for the regiochemistry and stereocontrol in the ring closure process. To this end, the benzoates **7** and **11** were prepared as enantiopure diastereomers via asymmetric allylations beginning with a C_2-substituted allylstannane and 3-phenylpropanal.[8]

Stereoselective formation of the *cis*-2,5-disubstituted tetrahydrofuran **8** occurred in 77% yield (8:1 cis:trans ratio) upon slow addition of alcohol **7** to a mixture of NaH (1 equiv), Me_3SnCl (1 equiv), and $Pd(OAc)_2/Ph_3P$ (20 mol %) catalyst in THF at 60 °C. The use of Me_3SnCl as an additive led to accelerated reactions and maintained a strongly nucleophilic oxygen for the ring closure event with suppression of a detrimental internal acyl migration.[9] Ether **8** arises via exclusive regiocontrol during the cyclization event. This is contrasted with the usual regiocontrol observed for soft carbon nucleophiles which encounter substantial steric interactions in the transition state.[10] The lengthy Sn−O bonding of the stannyl ether permits substitution at the more electrophilic allylic terminus of the Pd(0) complex while minimizing the steric component in the addition process.[7a] The retention of the C_6 geometry in **8** can be rationalized by a backside displacement of the C_6 benzoate by Pd(0) followed by a second backside replacement of palladium from the π-allyl complex **9**. To facilitate our stereochemical assignments by ^{1}H NMR spectroscopy, 2,5-*trans*-THF **10** was prepared by mesylation and benzoate saponification of **7** with ring closure and C_3 inversion (Scheme 1).[11] Similarly,

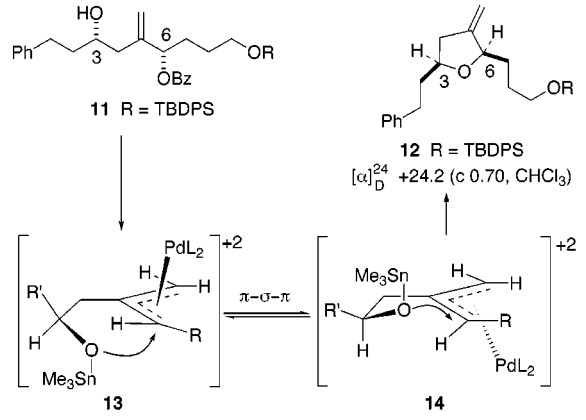
Scheme 1



the mesylation of *syn*-alcohol **11** and ester hydrolysis directly produced THF **8**, thereby confirming our stereochemical assignments.

Interestingly, the *syn*-1,4-diol derivative **11** cyclized under the palladium-catalyzed conditions in 73% isolated yield also affording an 8:1 ratio of *cis*- and *trans*-2,5-tetrahydrofurans. Characterization of the major isomer **12** established the antipodal relationship to **8**, indicating that the reaction to **12** proceeded with *net inversion* of C_6 stereochemistry. We have

Scheme 2



(7) For leading references, see: (a) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408. (b) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.

(8) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P. *Tetrahedron Lett.* **1998**, *39*, 7251.

(9) Inverse addition or direct combination of all reactants lead to 40−50% yields, prolonged reaction times, and substantial amounts of unreactive allylic alcohol resulting from internal transesterification. For further discussions, see: (a) Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, *50*, 3558. (b) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927.

(10) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

(11) Establishing stereochemical relationships in substituted tetrahydrofurans on the basis of ^{1}H NMR data can be exceedingly problematic. For a discussion of noteworthy features and related systems, see ref 4c and the following. (a) Mihelich, E. D.; Hite, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7318. (b) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995.

(12) Two stereochemical elements, which feature palladium in association with either face of cisoid and transoid π-allyl arrangements, lead to four diastereomeric complexes for each of the starting isomeric alcohols **7** and **11**. Our calculations indicate only a small energy difference (less than 1 kcal/mol) resulting from the 1,2- versus 1,3-interactions in **A** and **B**, respectively. Pairs of diastereomeric η^3 complexes lead to our *cis*- and *trans*-2,5-tetrahydrofuran products. However, cyclizations proceeding from isomers as exemplified in *i* and *ii* are less favorable than those depicted from **9** and **14** owing to the development of 1,3-nonbonded interactions in transition states leading to C−O bond formation.

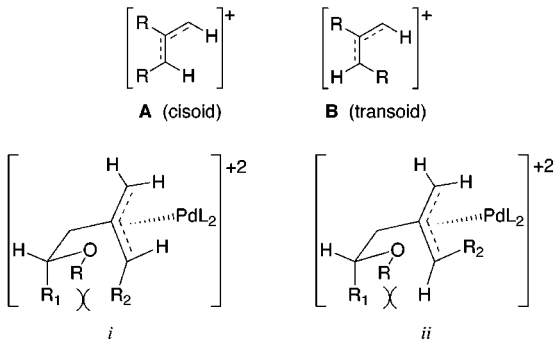
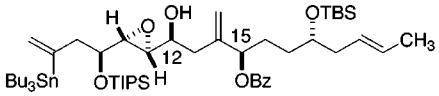
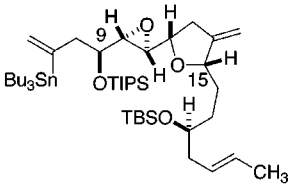
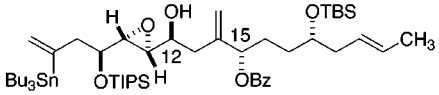
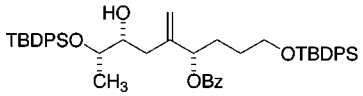
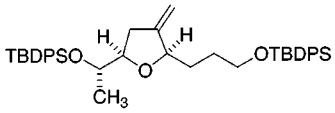
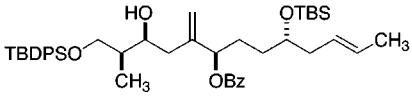
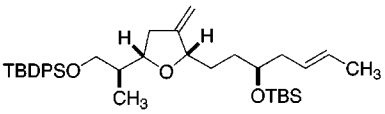
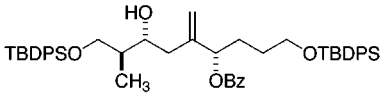
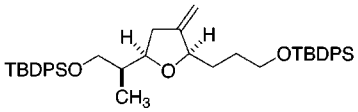
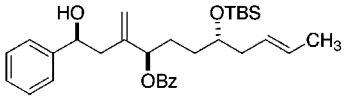
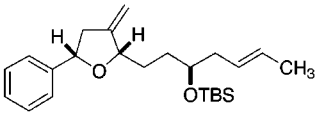


Table 1. Palladium-Induced Cyclizations

entry	substrate	product	% yield[a]	dr (*cis*:*trans*)[b]
1			88[c]	13 : 1
2			71[c]	12 : 1
3			62[c]	8.5 : 1
4			68[d]	5.3 : 1
5			70[c]	3 : 1
6			96[d]	3 : 1

[a] Purified yields [b] Determined from ^{1}H-NMR (400 MHz) data of crude mixtures [c] $Pd(OAc)_2/Ph_3P$ (0.2 equiv), NaH (1 equiv), Me_3SnCl (1 equiv) in THF at 60 °C [d] $Pd(PPh_3)_4$ (0.2 equiv), NaH (1 equiv), Me_3SnCl (1 equiv) in THF at 60 °C

concluded that nonbonded 1,3-interactions arising in the transition state for ring closure favor production of *cis*-2,5-disubstituted products. Prior to cyclization, formation of four diastereomeric η^3 complexes are feasible from allylic benzoate **11**.[12] However, as illustrated for **13**, the cyclization suffers from developing 1,3-steric interactions (R;H), whereas the alternative backside displacement in **14** features a 1,3-diequatorial disposition of carbon substituents (Scheme 2). Isomerization to **14** is presumably achieved via carbon bond rotations of putative σ-bound palladium intermediates. The 3-methylenetetrahydrofurans are kinetic products which do not undergo isomerization upon resubmission to the reaction conditions.

The cyclization conditions are generally applicable and accommodate additional functionality (Table 1). The C_7-C_{22} fragment of amphidinolide K (**1**) was successfully obtained from either the *syn*-1,4-precursor via C_{15} inversion (entry 1) or C_{15} net retention (entry 2). Adjacent stereochemistry, particularly in the vicinal *syn*-arrangement as shown in entries 3 and 4, was well tolerated. However, steric requirements in entry 5 and aryl substitution (entry 6) led to an erosion of the observed preference for *cis*-product.

In summary, we have described a cyclization of 2-methylene-1,4-diol monobenzoates to afford 3-methylenetetrahydrofurans with exclusive regiocontrol. The palladium-catalyzed ring closure proceeds stereoselectively to provide *cis*-2,5-disubstituted products. This methodology has facilitated the preparation of the C_7-C_{22} fragment of amphidinolide K, and further efforts for the total synthesis of **1** will be reported in due course.

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