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A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives via Sequential Asymmetric Horner–Wadsworth–Emmons and Palladium-Catalyzed Ring Closure Reactions

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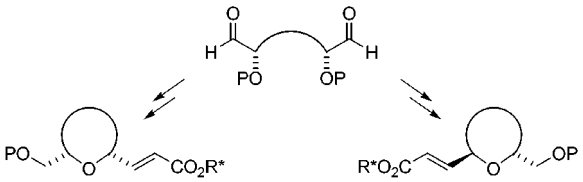
ABSTRACT



An approach to chiral tetrahydrofuran and tetrahydropyran derivatives is reported which is based on the sequential use of an asymmetric Horner–Wadsworth–Emmons desymmetrization of a *meso*-dialdehyde and a palladium-catalyzed intramolecular allylic substitution. The strategy is versatile in that either a *cis*- or a *trans*-relation between the stereocenters adjacent to the ring oxygen can be obtained.

The development of stereoselective syntheses of substituted tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives is an important challenge because of the frequent occurrence of such oxacycles as substructures in biologically active substances, such as the annonaceous acetogenins[1] and several groups of macrolides.[2] The need for appropriately functionalized synthetic building blocks has motivated the development of many different synthetic approaches.[3] In this Letter, we describe a stereochemically versatile approach to certain

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(3) For reviews, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. Selected recent examples: (c) Berninger, J.; Koert, U.; Eisenberg-Höhl, C.; Knochel, P. *Chem. Ber.* **1995**, *128*, 1021, and references therein. (d) Ramírez, M. A.; Padrón, J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584, and references therein. (e) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076, and references therein. (f) Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E.; Wadsworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2259. (g) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792. (h) Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53. (i) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461.

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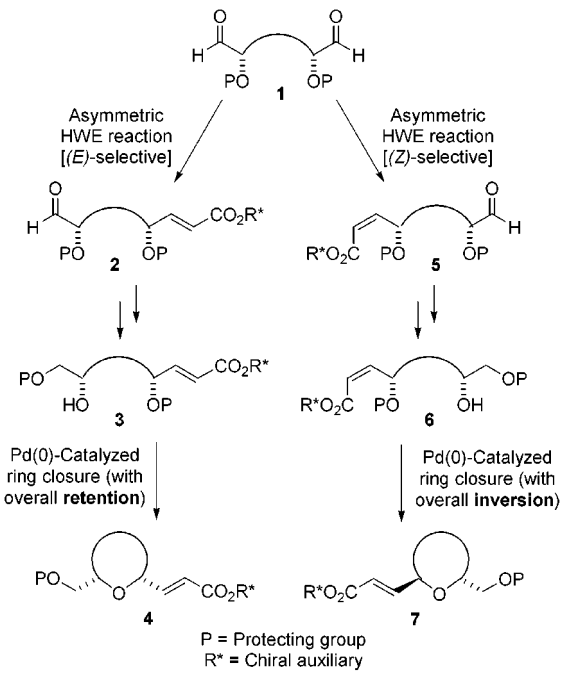
THF and THP derivatives which is based on the sequential use of an asymmetric Horner−Wadsworth−Emmons (HWE) reaction[4] and an intramolecular palladium-catalyzed allylic substitution.[5] An attractive feature of this approach is the fact that as a result of the stereospecificity of the Pd(0)-catalyzed reaction, control of the alkene geometry in the HWE product translates into control of the relative configuration of the ring-closed product.

We have recently reported that *meso*-dialdehydes of type **1** can be efficiently desymmetrized by use of asymmetric HWE reactions[4g] to give either (*E*)-alkenes **2** or (*Z*)-alkenes **5** with good to excellent levels of geometric selectivity and asymmetric induction. The protective group P can be chosen so that the PO group can act as a leaving group in a Pd(0)-catalyzed allylic substitution[6] (Scheme 1). After reduction

Scheme 1



of the unreacted formyl group in the HWE product, migration of the one protective group P which is adjacent to the primary alcohol will give compounds **3** and **6**, respectively, in which the stage is now set for a Pd(0)-catalyzed ring closure in which the liberated secondary OH group can act as the nucleophile. In general, (*E*)-allylic substrates are known to undergo Pd(0)-catalyzed substitution with O-nucleophiles with overall *retention* of configuration; (*Z*)-allylic compounds, on the other hand, might undergo a $\pi-\sigma-\pi$ rearrangement of the intermediate palladium complex before the nucleophilic attack takes place, resulting in overall *inversion* of configuration and simultaneous conversion of the (*Z*)-alkene to an (*E*)-alkene.[7] We therefore anticipated a possibility for versatility of stereocontrol: whereas (*E*)-substrates **3** would give *cis*-products **4**, ring closure of (*Z*)-substrates **6** could provide access to *trans*-products **7**. Precedence for ring closure by Pd(0)-catalyzed allylic substitution with an oxygen nucleophile does exist,[5] but the opportunities for simultaneously controlling the stereochemistry to obtain, at will, either retention or inversion of configuration appear to be previously unexplored.

To apply this strategy to the preparation of THF derivatives, we investigated asymmetric HWE reactions with *meso*-dialdehyde **8**[8] (Scheme 2). Pivaloyl protective groups were chosen because allylic carboxylates are known to be good precursors of η^3-allylpalladium complexes. To our delight, asymmetric HWE reactions between **8** and phosphonates **9** gave essentially complete geometric selectivities as well as excellent diastereoselectivities.[9,10]

Subsequent reduction of the aldehyde functionalities in **10** and **14**, followed by acyl group migration, gave **12** and **16**, respectively.[11] When compound **12** was treated with catalytic amounts of $Pd_2(dba)_3$ in the presence of neocuproine,[12] it readily ring-closed at room temperature to give the 2,5-*cis*-disubstituted THF derivative **13**,[13] with complete retention of configuration at the allylic stereocenter.

The (*Z*)-alkene **16**, on the other hand, required elevated temperatures (refluxing THF) under otherwise similar condi-

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(6) For a general reference, see: Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley & Sons: New York, 1995; pp 290−340.

(7) For examples, see: (a) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (b) Sugiura, M.; Yagi, Y.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 4351.

(8) See Supporting Information for details on how compound **8** was prepared.

(9) Both geometric selectivities and diastereomer ratios for the HWE products were determined by ^{1}H NMR spectroscopy. The absolute configurations of compounds **12** and **16** were assigned on the basis of NMR analyses of the corresponding Mosher esters (see Supporting Information for details).

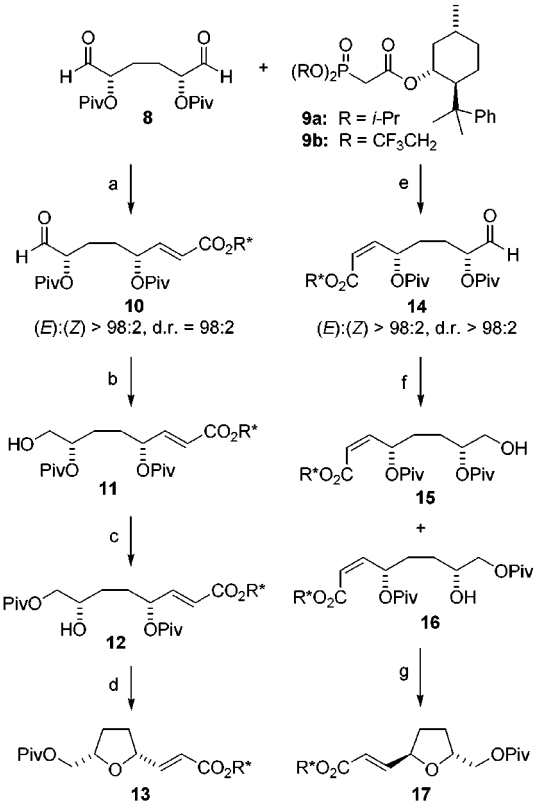
(10) From the reaction between **8** and **9a**, bisaddition products were also isolated in ca. 40% yield, which explains the modest yield of compound **10**.

(11) Depending on the specific conditions used, varying ratios between the secondary alcohols (**12**, **16**, **20**, and **23**) and the isomeric primary alcohols (**11**, **15**, **19**, and **22**, respectively) could be obtained from reduction of the corresponding HWE products. The primary alcohols could be separated and converted to mixtures of secondary/primary, thereby increasing the overall yield of the desired secondary alcohols to ca. 70% after one iteration (see Supporting Information for details).

(12) Neocuproine = 2,9-dimethyl-1,10-phenanthroline.

(13) Assignments of relative configuration in the ring-closed products are based on NOE experiments on compounds **13**, **17**, and **24**. The assignment for compound **21** is based on ^{13}C NMR analysis of a derivative (see Supporting Information for details).

Scheme 2[a]



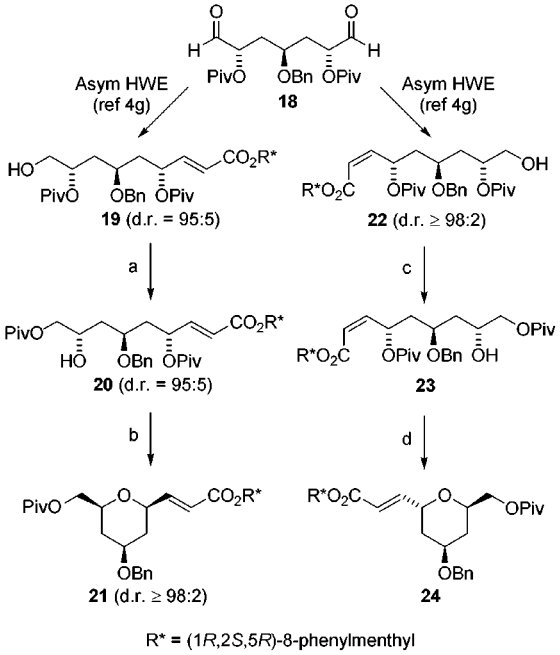
[a] Reaction conditions: (a) 1.3 equiv of **8**, 1.1 equiv of **9a**, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, THF, −85 °C; 55%; (b) $NaBH_4$, MeOH/THF, 0 °C; 85%; (c) DMAP, EtOH, 75 °C; 63% **12**, 27% recovered **11** (see footnote 11); (d) $Pd_2(dba)_3$·$CHCl_3$ (0.05 equiv), neocuproine (0.2 equiv), THF, 25 °C; 76%; (e) 1.3 equiv of **8**, 1.1 equiv of **9b**, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, THF, −85 °C; 71%; (f) $LiBH_4$, *i*-PrOH/THF, 0 °C; 49% **16**, 38% **15** (see footnote 11); (g) $Pd_2(dba)_3$•$CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 65 °C; 79%.

tions for the ring closure to occur. The major product was the 2,5-*trans*-disubstituted THF derivative **17**,[13] containing an (*E*)-alkene, an outcome which is completely consistent with the anticipated $\pi-\sigma-\pi$ rearrangement. Use of phosphine ligands in place of neocuproine in reactions with **16** caused elimination to form a diene to prevail over the desired ring closure.

Starting from compounds **19** and **22**, which are available via asymmetric HWE desymmetrization of *meso*-dialdehyde **18** followed by $NaBH_4$ reduction,[4g] THP derivatives **21** and **24** were synthesized using a similar approach (Scheme 3).

Pivaloyl group migration afforded the secondary alcohols **20** and **23** from **19** and **22**, respectively.[11] When the (*E*)-alkene **20** was subjected to the ring closure conditions, we were pleased to see that the desired 2,6-*cis*-THP derivative **21** could be obtained diastereomerically pure, even though the starting material **20** contained minor amounts (ca. 5%) of another isomer. Ring closure of the (*Z*)-alkene **23** gave, as expected, the 2,6-*trans*-derivative **24**, in analogy to the formation of compound **17** from **16**.

Scheme 3[a]



[a] Reaction conditions: (a) imidazole, EtOH, 75 °C; 59% **20**, 28% recovered **19** (see footnote 11); (b) $Pd_2(dba)_3$·$CHCl_3$ (0.1 equiv), neocuproine (0.4 equiv), THF, 25 °C; 80%; (c) DMAP, EtOH, 75 °C; 48% **23**, 42% recovered **22** (see footnote 11); (d) $Pd_2(dba)_3$•$CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 50 °C; 59%.

To summarize, we have demonstrated efficient stereocontrolled routes for the preparation of various functionalized THF and THP derivatives, using a strategy involving an asymmetric HWE reaction in sequence with a palladium-catalyzed intramolecular allylic substitution as key steps. The relative configuration of the stereocenters adjacent to the ring oxygen is controlled by the combined influence of the geometric selectivity of the HWE reaction and the stereospecificity of the palladium-catalyzed process, while the absolute configuration is controlled in the asymmetric HWE reaction. We are currently investigating possible extensions of this strategy to the preparation of other heterocyclic and carbocyclic systems.

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

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