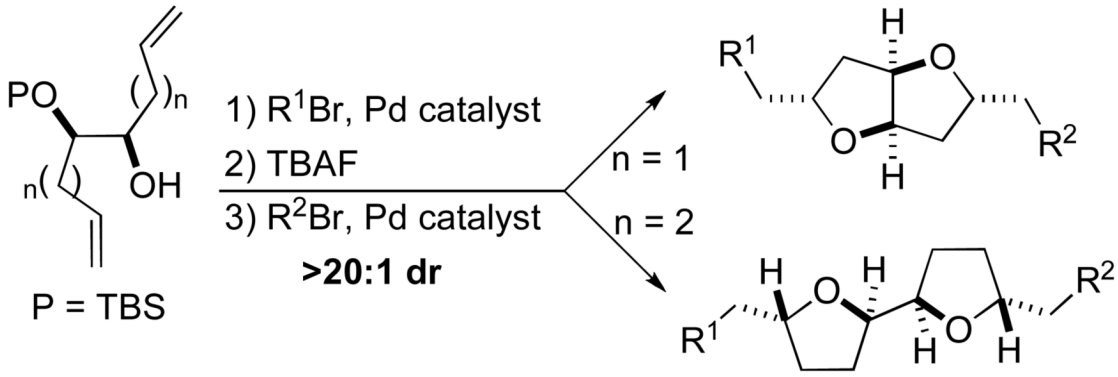
Published in final edited form as:
Org Lett. 2009 May 21; 11(10): 2209–2212. doi:10.1021/ol900594h.

Synthesis of Fused-Ring and Attached-Ring bis-Tetrahydrofurans via PdCatalyzed Carboetherification

Amanda F. Ward and **John P. Wolfe***
Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan, 48109-1055

Abstract



A five step-synthesis of fused bis-tetrahydrofurans and attached bis-tetrahydrofurans from butadiene diepoxide is described. Two sequential Pd-catalyzed carboetherification reactions between protected 1,2-diols and aryl/alkenyl bromides, each of which form both a C–O bond and a C–C bond, are used to generate the heterocyclic rings with >20:1 dr. Installation of different R^1 and R^2 groups is achieved in a straightforward fashion through use of different aryl or alkenyl bromide coupling partners.

A large number of interesting compounds contain attached-ring or fused-ring tetrahydrofuran scaffolds (Figure 1). The 2,6-dioxabicyclo[3.3.0]octane framework (**1**) is found in both naturally occurring[1] and synthetic molecules that are relevant to human health (e.g., **3**; antitumor activity)[2] and agriculture (e.g., **4**; herbicide).[3] Attached-ring tetrahydrofurans (**2**) are displayed in a vast number of natural products, including the annonaceous acetogenins,[4] of which asimicin (**5**) is a member.

A variety of different approaches have been developed for the construction of these useful compounds.[4,5] Many of these strategies involve generation of the *bis*-tetrahydrofuran framework via sequential (or tandem) ring-closing reactions of 1,2-diols bearing pendant functional groups such as alkenes, epoxides, alcohols, or allylic acetates/halides.[6] Although these methods effectively form the heterocyclic ring, they do not allow the simultaneous construction of a C–C bond. Thus, substituents attached to the tetrahydrofuran C2-position, such as the side chains present in **3**–**5**, must be installed in separate steps either prior to or following ring-closure.

E-mail: jpwolfe@umich.edu.

Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds reported in the text (128 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

We felt that an alternative approach to the construction of substituted fused-ring tetrahydrofurans with the general structure **8** could be developed using sequential Pdcatalyzed carboetherification reactions[7,8] of unsaturated 1,2-diols such as **6**. As shown in Scheme 1, treatment of **6** with an aryl or alkenyl halide in the presence of NaO*t*Bu and a palladium catalyst should provide **7**, which could be converted to **8** in a second catalytic transformation. This strategy could also be applied to the synthesis of attached-ring tetrahydrofurans (e.g., **9** to **10**) by simply extending the tether between the alcohols and the alkenes by one methylene unit. Importantly, each carboetherification reaction would generate both a C–O bond (to form the heterocylic ring) *and a C–C bond*, thus providing a more concise approach to substituted *bis*-tetrahydrofurans compared to currently available methods.

In order to examine the feasibility of the strategy outlined above, we elected to examine the selective monocyclization of known diols **6**[6i] and **9**,[9] which can be generated by Cu-catalyzed addition of vinylmagnesium bromide or allylmagnesium bromide to commercially available butadiene diepoxide. We also prepared *mono*-TBS-protected[10] derivatives **11** and **12** (Figure 2), as our prior studies indicated that carboetherification reactions of *mono*-protected 1,2-diols are often more efficient than transformations of the corresponding unprotected diols.[8]

Preliminary attempts to effect selective monocyclization of unprotected diols **6** and **9** provided unsatisfactory results (Figure 3). Treatment of **6** with one equivalent of bromobenzene under our standard carboetherification conditions (NaO*t*Bu, cat. Pd_2 $(dba)_3$/Dpe-Phos)[11] afforded mixtures of *bis*-cyclized product **13** and unreacted starting material. Treatment of **6** with four equivalents of bromobenzene led to complete consumption of starting material and the formation of **13** with >20:1 dr, albeit in only 30% yield. Efforts to achieve monocyclization of **9** did lead to the formation of desired tetrahydrofuran **14**, but yields were low and isomerization of the second alkene was problematic. Use of excess aryl halide in this reaction failed to generate significant amounts of the *bis*-tetrahydrofuran target, and instead provided an 81% combined yield of **14** and inseparable alkene isomers.

Although carboetherification reactions of **6** and **9** were generally ineffective, transformations of TBS-protected substrates **11** and **12** proceeded smoothly. As shown in Table 1, treatment of **11** with an aryl bromide in the presence of NaO*t*Bu and a catalyst composed of $Pd_2(dba)_3$ and Dpe-Phos provided tetrahydrofurans **15** in good yields with excellent diastereoselectivities. Cleavage of the silyl ether protecting group was achieved under standard conditions, and carboetherification of the resulting alcohols **16** provided fused tetrahydrofurans (**8**) as single stereoisomers (>20:1 dr). Both cyclizations led to products that are *trans*−2,5-disubstituted around the tetrahydrofuran ring(s), which is consistent with our previously reported observations and stereochemical models for the conversion of γ-hydroxy alkenes to tetrahydrofurans.[8]

The first carboetherification reaction in this sequence (**11** to **15**) was sensitive to the electronic properties of the aryl bromide, and the best yields were obtained with electron-neutral substrates (entries 1–6). However, the scope of the second carboetherification reaction (**16** to **8**) was much broader, and a number of different aryl bromides were effectively coupled. In addition, use of β-bromostyrene in the second transformation was also successful (entry 7). Diastereoselectivities were uniformly high in all of the carboetherification reactions (>20:1 dr), and in many cases the overall yield of **8** exceeded 50% over the three-step sequence.

The synthesis of attached-ring *bis*-tetrahydrofurans was achieved by subjecting protected diol **12** to an analogous sequence of carboetherification (**12** to **17**), deprotection (**17** to **18**), and carboetherification (**18** to **10**). As observed in the transformations of **11**, the scope of the second carboetherification step is considerably broader than the first (with respect to the aryl bromide component). Yields of attached-ring tetrahydrofurans were slightly lower than the

corresponding fused-ring products described above. However, diastereoselectivities were excellent, and all products were obtained with >20:1 dr favoring 2,5-*trans*-stereochemistry around both tetrahydrofuran rings.

To further probe the synthetic utility of these transformations, we sought to determine if nonracemic starting materials could be converted to *bis*-tetrahydrofuran products without loss of enantiomeric purity. To this end, (–)−**12** was prepared in 96% ee via asymmetric dihydroxylation of commercially available *trans*−1,5,9-decatriene[12] followed by *mono*-TBS-protection of the resulting diol. This substrate was converted to (–)−**10h** using a sequence of reactions identical to that shown in Table 2, entry 8, and the product was obtained with >20:1 dr and 95% ee (Figure 4).

The synthesis of more elaborate tetrahydrofuran products is also feasible using this method. For example, protected tetraol derivative **19** was generated from Dmannitol using standard transformations.[13] This substrate was converted to *bis*-tetrahydrofuran **22** with >20:1 dr using the same reaction sequence described above (Scheme 2).

In conclusion, we have developed a concise approach to the construction of both attached-ring and fused-ring *bis*-tetrahydrofurans using sequential Pd-catalyzed carboetherification reactions. This strategy allows for preparation of derivatives bearing different substituents at the 2-position of each tetrahydrofuran ring, and provides access to derivatives that could not be easily generated with existing methods. Further studies on the application of these reactions to the synthesis of natural products and molecules of medicinal interest are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors thank the NIH-NIGMS (GM071650) for financial support of this work. Additional support was provided by the Camille and Henry Dreyfus Foundation (Camille Dreyfus Teacher Scholar Award), GlaxoSmithKline, Eli Lilly, Amgen, and 3M. The authors also thank Ms. Jody Canapp for performing preliminary experiments in this area.

References

1. (a) Suzuki T, Koizumi K, Suzuki M, Kurosawa E. Chem. Lett 1983:1639–1642. (b) Suzuki M, Kurosawa E. Phytochemistry 1985;24:1999–2002.
2. Pinacho Cisostomo FR, Padron JM, Martin T, Villar J, Martin VS. Eur. J. Org. Chem 2006:1910–1916.
3. Kakimoto T, Koizumi F, Hirase K, Arai K. J. Pestic. Sci 2006;31:380–389.
4. For recent reviews, see: (a)McLaughin JL. J. Nat. Prod 2008;71:1311–1321.1321 [PubMed: 18598079] (b)Bermejo A, Figadere B, Zafra-Polo M-C, Barrachina I, Estornell E, Cortes D. Nat. Prod. Rep 2005;22:269–303.303 [PubMed: 15806200] (c)Alali FQ, Liu X-X, McLaughlin JL. J. Nat. Prod 1999;62:504–540.540 [PubMed: 10096871]
5. For general reviews on the synthesis of tetrahydrofurans, see: (a)Wolfe JP, Hay MB. Tetrahedron 2007;63:261–290.290 [PubMed: 18180807] (b)Harmange J-C, Figadere B. Tetrahedron: Asymmetry 1993;4:1711–1754.1754
6. For representative examples of attached-ring tetrahydrofuran synthesis, see: (a)Li P, Wang T, Emge T, Zhao K. J. Am. Chem. Soc 1998;120:7391–7392.7392 (b)Hoye TR, Ye Z. J. Am. Chem. Soc 1996;118:1801–1802.1802 (c)Wysocki LM, Dodge MW, Voight EA, Burke SD. Org. Lett 2006;8:5637–5640.5640 [PubMed: 17107091] (d)Marshall JA, Sabatini JJ. Org. Lett 2006;8:3557–3560.3560 [PubMed: 16869659] (e)Carlisle J, Fox DJ, Warren S. Chem. Commun 2003:2696–2697.2697 (f)Sinha A, Sinha SC, Keinan E. J. Org. Chem 1999;64:2381–2386.2386 (g)Beauchamp TJ, Powers JP, Rychnovsky SD. J. Am. Chem. Soc 1995;117:12873–12874.12874 For representative examples of fused-ring tetrahydrofuran synthesis, see: (h) Reference 2. (i)Wang J, Pagenkopf BL. Org.

Lett 2007;9:3703–3706.3706 [PubMed: 17691801] (j)Duclos A, Fayet C, Gelas J. Synthesis 1994:1087–1090.1090

7. For reviews see: (a)Wolfe JP. Eur. J. Org. Chem 2007:571–582.582 (b)Wolfe JP. Synlett 2008:2913–2937.2937
8. (a) Wolfe JP, Rossi MA. J. Am. Chem. Soc 2004;126:1620–1621. [PubMed: 14871078] (b) Hay MB, Hardin AR, Wolfe JP. J. Org. Chem 2005;70:3099–3107. [PubMed: 15822970] (c) Hay MB, Wolfe JP. J. Am. Chem. Soc 2005;127:16468–16476. [PubMed: 16305233] (d) Hay MB, Wolfe JP. Tetrahedron Lett 2006;47:2793–2796.
9. Baylon C, Heck M-P, Mioskowski C. J. Org. Chem 1999;64:3354–3360. [PubMed: 11674445]
10. Essenfeld AP, Gillis HR, Roush WR. J. Org. Chem 1984;49:4674–4682.
11. Dpe-Phos = *bis*(2-diphenylphosphinophenyl)ether.
12. Braddock DC, Cansell G, Hermitage SA, White AJP. Tetrahedron: Asymmetry 2004;15:3123–3129.
13. (a) Kajiwara M, Miyazawa M, Nakazawa M, Shimayama T, Takatori K, Takahashi T, Yamada H. Tetrahedron Lett 1992;33:5973–5976. (b) Depezay JC, Duréault A, LeMerrer Y, Greck C, Micas-Languin D, Gravier C. Heterocycles 1987;25:541–548.

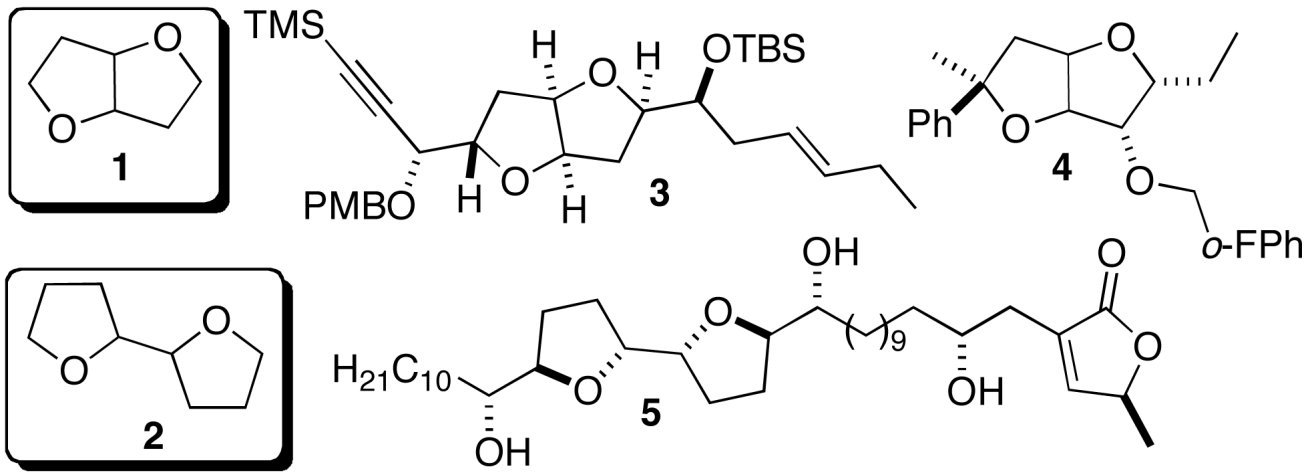
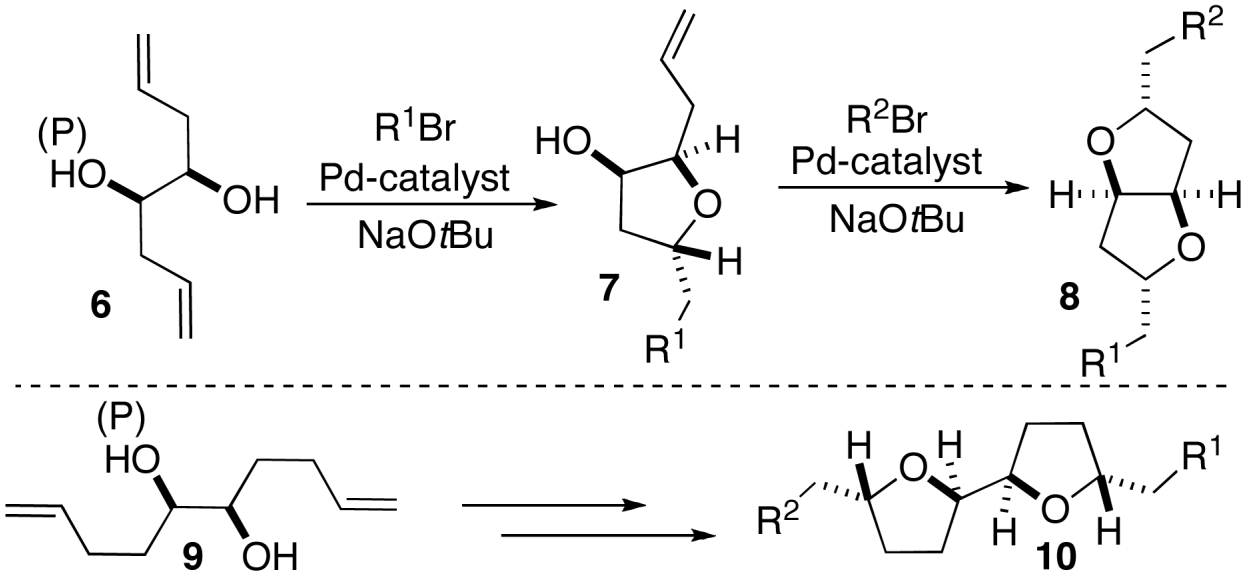
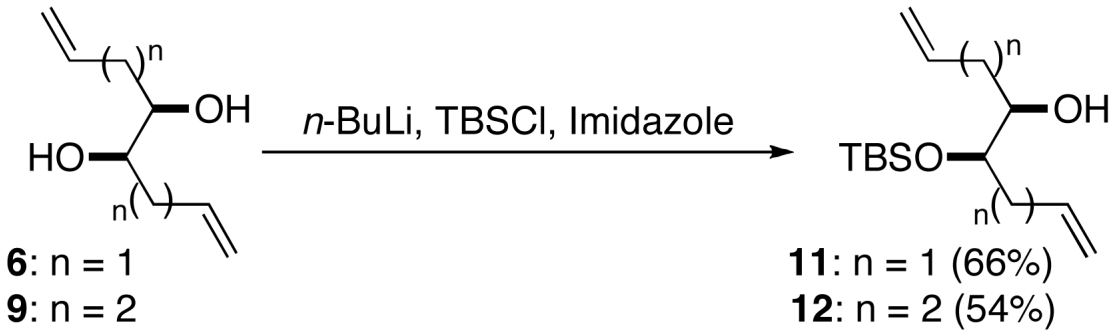


Figure 1.
Examples of Biologically Active *bis*-Tetrahydrofurans



Scheme 1.
Synthetic Strategy



6: n = 1
9: n = 2

11: n = 1 (66%)
12: n = 2 (54%)

Figure 2.
Protection of 1,2-Diols

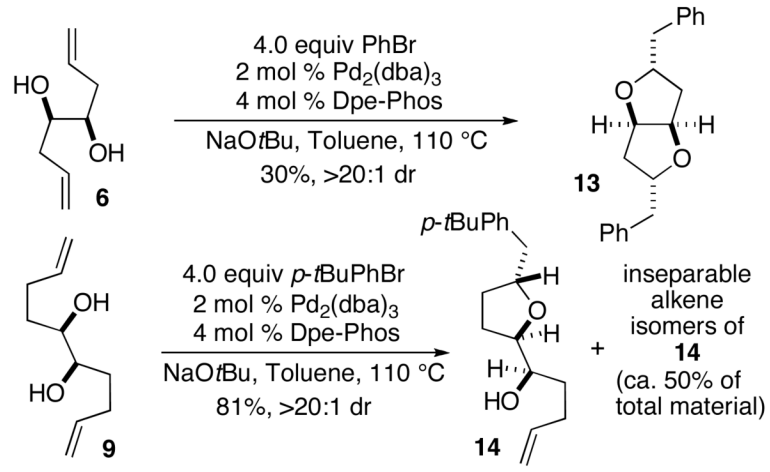


Figure 3.
Attempted Monocyclization of 1,2-Diols

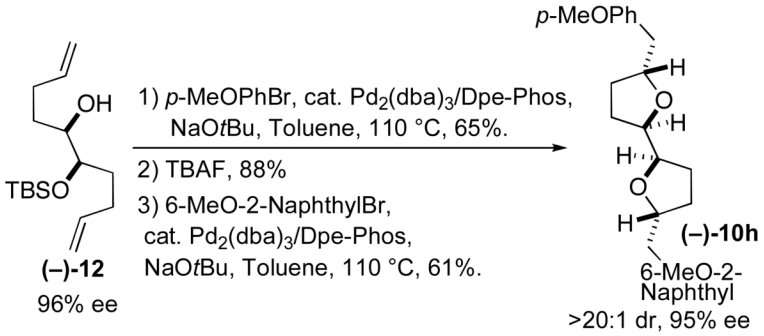
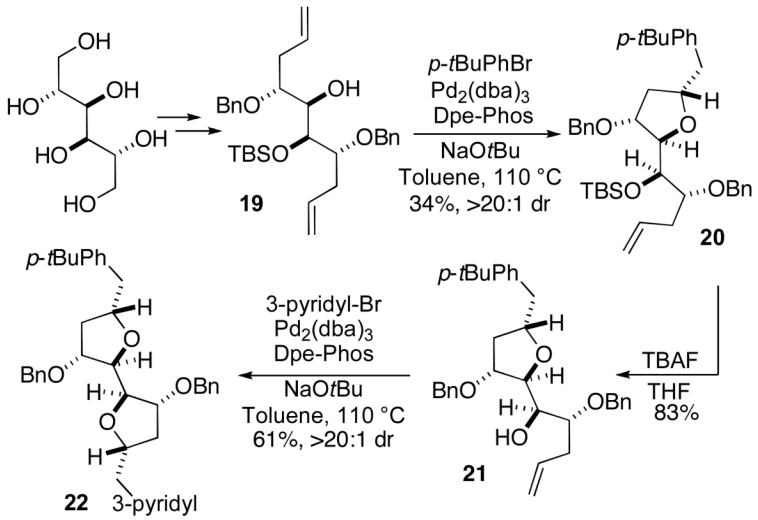


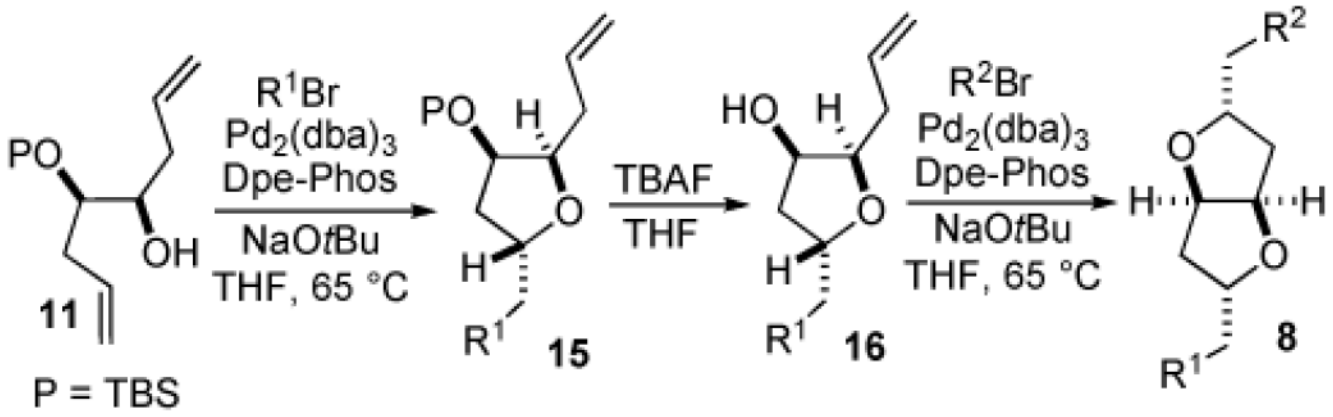
Figure 4.
Synthesis of an Enantioenriched *bis*-Tetrahydrofuran



Scheme 2.
Synthesis of a Highly Substituted *bis*-Tetrahydrofuran

Table 1

Stepwise Synthesis of Fused Tetrahydrofurans[a]



entry	R^1	yield 15 (%)[b]	yield 16 (%)[b]	R^2	yield 8 (%)[b]	overall yield (%)[c]
1	Ph	86	92	*p*-F_3CPh	86	68
2				*p*-PhC(O)Ph	94	74
3	*p*-Tol	91	91	3-pyridyl	91	75
4				*m*-MeOPh	81	67
5	*p*-*t*BuPh	71	90	*p*-PhPh	87	43
6				2-naphthyl	85	54
7	*p*-PhC(O)Ph	44	92	(*E*)-β-styryl	67	27
8				6-MeO-2-naphthyl	89	36

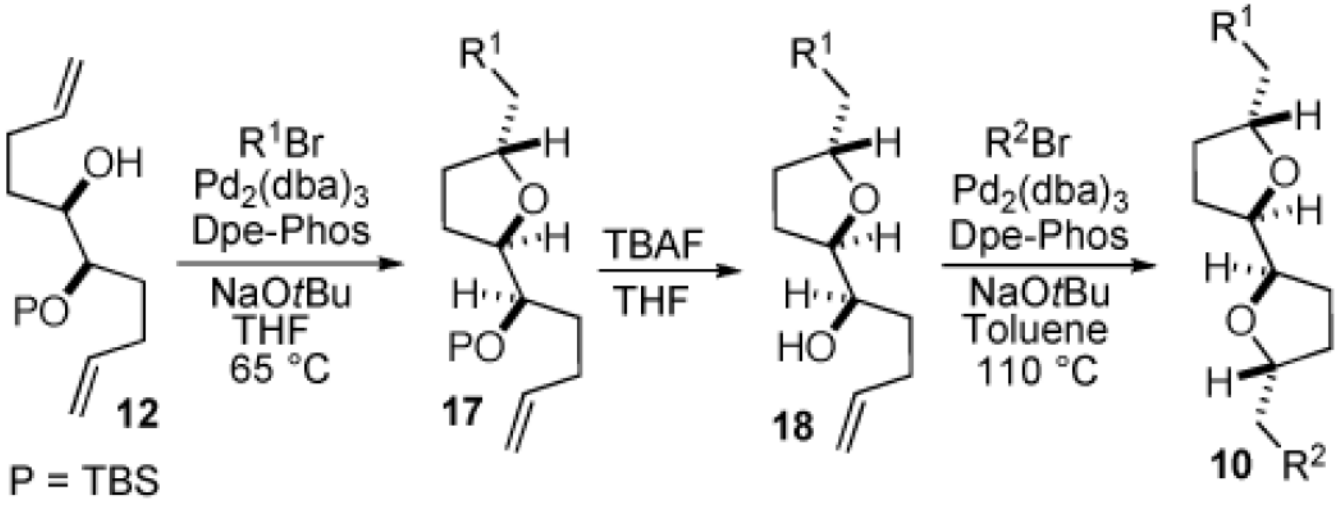
[a] Conditions: Steps 1 and 3: 1.0 equiv **11** or **16**, 2.0 equiv ArBr, 2.0 equiv NaO*t*Bu, 2 mol % $Pd_2(dba)_3$, 4 mol % Dpe-Phos, THF, 65 °C. Step 2: 1.0 equiv **15**, 10 equiv TBAF, THF, rt.

[b] Isolated yields (average of two or more experiments). All products were obtained with >20:1 dr.

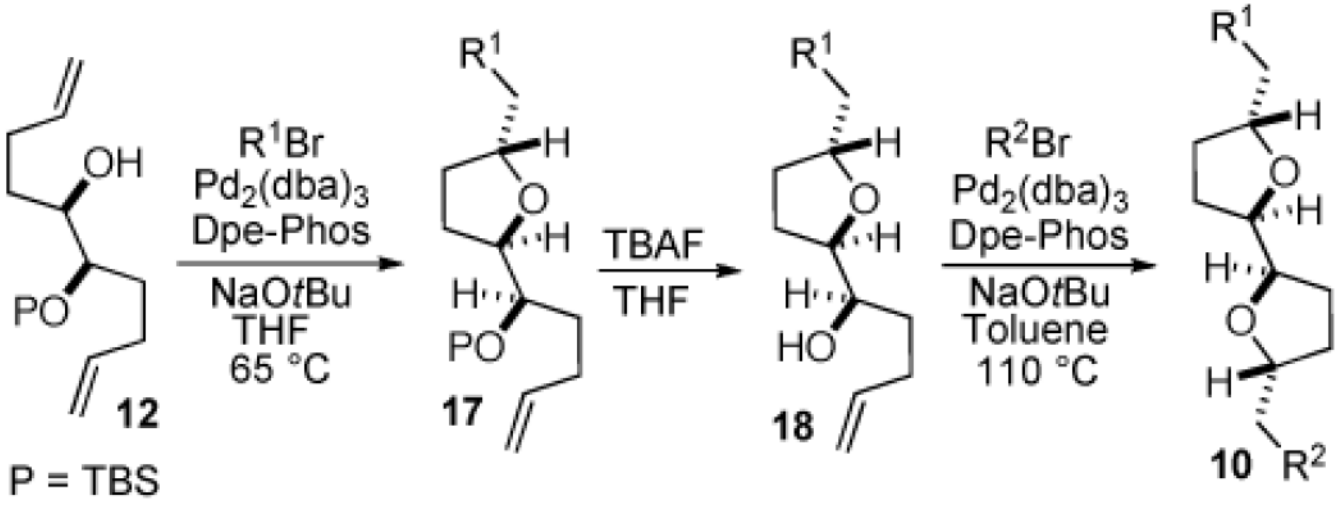
[c] Yield obtained over the three step sequence from **11** to **8**.

Table 2

Stepwise Synthesis of Attached Tetrahydrofurans[a]



entry	R^1	yield 17 (%)[b]	yield 18 (%)[b]	R^2	yield 10 (%)[b]	overall yield (%)[c]
1	*p*-*t*BuPh	73	89	*p*-Tol	64	42
2				*p*-PhPh	63	41
3	Ph	72	91	3-pyridyl	54	35
4				2-naphthyl	61	40
5	*m*-MeOPh	64	91	*p*-F_3CPh	75	44
6				*p*-PhC(O)Ph	72	42
7	*p*-MeOPh	55	96	3,5-Cl_2Ph	71	37



entry	R^1	yield 17 (%)[b]	yield 18 (%)[b]	R^2	yield 10 (%)[b]	overall yield (%)[c]
8				6-MeO-2-naphthyl	53	28

[a] Conditions: Steps 1 and 3: 1.0 equiv **12** or **18**, 2.0 equiv ArBr, 2.0 equiv NaO*t*Bu, 2 mol % $Pd_2(dba)_3$, 4 mol % Dpe-Phos, Toluene or THF, 65 °C or 110 °C. Step 2: 1.0 equiv **17**, 10 equiv TBAF, THF, rt.

[b] Isolated yields (average of two or more experiments). All products were obtained with >20:1 dr.

[c] Yield obtained over the three step sequence from **12** to **10**.