# A Cycloisomerization Approach to Tetrahydrofurans

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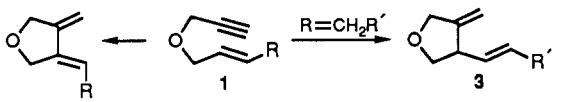
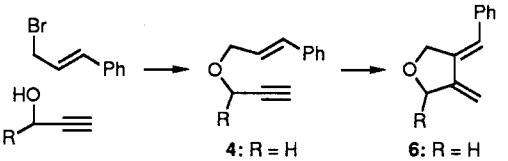
*Summary:* The development of novel catalysts for enyne cyclizations combined with facile ways to generate allylpropargyl ethers provide ready access to usefully functionalized tetrahydrofurans of use for construction of polyhydrofuryl natural ligands like furofurans and podophyllotoxin and especially polyhydrobenzofurans represented by phyllanthocin.

*Sir:* The increasing incidence of polyhydrofurans either as the key entity itself or as a key substructure of a more complex molecule in various biologically interesting natural products creates a need for diverse synthetic strategies. A cycloisomerization[1,2] has the advantage of enhanced efficiency. We, therefore, undertook a study of the cyclization of enynes of type **1** under the influence of palladium catalysis directed toward both 1,3-dienes of type **2**, which may provide a facile entry to polyhydrofuryl natural lignans (e.g. furofurans,[3] podophyllotoxins,[4] etc.), whose biological activity includes insecticidal and central nervous stimulatory and depressive effects, and 1,4-dienes of type **3** which may provide access to antitumor agents represented by phyllanthocin and the polyhydrobenzofuran subunit of the antiparasitic agent invermectin and related macrolides such as the milbemycins.[5]




**2** **1** **3**

As our models for the transformation of **1** to **2**, we chose the phenylated systems **4**[6] and **5**,[6] which are readily prepared by O-alkylation of the appropriate propargyl alcohol with cinnamyl bromide under phase-transfer conditions (50% aqueous NaOH, 5.5% TBAC, hexane, room temperature, 80–86%). The $Pd^{2+}$ catalyzed cycloisomerization to the 3,4-dialkylidenetetrahydrofuran showed a strikingly different sensitivity to choice of ligands compared to other types of substrates.[1] For example, *N,N'*-bis(benzylidene)ethylenediamine (BBEDA) previously proved to be the most useful ligand,[7] but its use for the reactions of eq 1

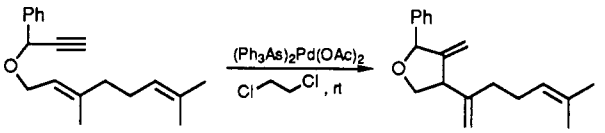



(1)

**4**: R = H
**5**: R = Ph
**6**: R = H
**7**: R = Ph

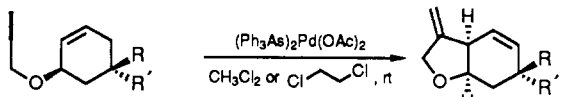
led only to recovered starting material. A catalyst generated in situ from triphenylphosphine and palladium acetate in chloroform or methylene chloride at 60 °C or 40 °C provided the very sensitive dialkylidenetetrahydrofurans **6** and **7** in 44% and 48% yields, respectively. A dramatic improvement occurred when the preformed complex bis(triphenylarsine)palladium acetate[8] was employed. Performing the reaction at room temperature or slightly above (40 °C) produces the sensitive dienes **6**[6] and **7**[6] in 73% and 96% yields, respectively. The sensitivity of the dienes both during reaction and workup is an important yield-determining factor. With the arsine ligand, which permits reaction at lower temperatures, and a rapid workup,[9] excellent yields are obtained.

As a useful model for the transformation of **1** to **3**, we applied the above conditions to the three substrates **8**,[6] **9**,[6] and **10**,[6] which provided selectively the alkenylmethylidenetetrahydrofurans **11**–**13**[6] (eq 2 and 3). The success of the latter cyclizations immediately led us to examine a more elaborate example directed toward the aglucone of the important antitumor agent phyllanthoside[10] known as phyllanthocin.[11,12]




(2)

**8** **11**




(3)

**9**: R = $CH_2OTBDPS$; R' = H
**10**: R = H; R' = $CH_2OTBDPS$

**12**
**13**

The requisite substrates **17**[6] and **18**[6] were synthesized by a novel mild mixed ketalization between the sensitive lactol **14** and the hydroxy esters **15** and **16** using K 10

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(6) This compound has been fully characterized spectrally and elemental composition established by high-resolution mass spectroscopy and/or combustion analysis.

(7) Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. unpublished work. Also see: Trost, B. M.; Jebaratnam, D. J. *Tetrahedron Lett.* **1987**, *28*, 1611.

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(9) The reaction mixture is directly and rapidly flash chromatographed using 3:2 hexane–dichloromethane to give the pure products.

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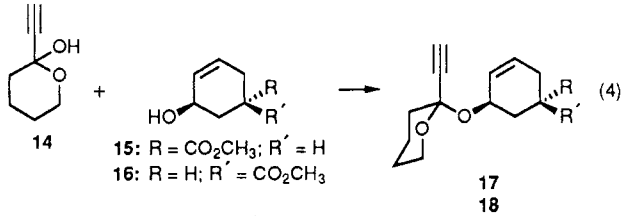
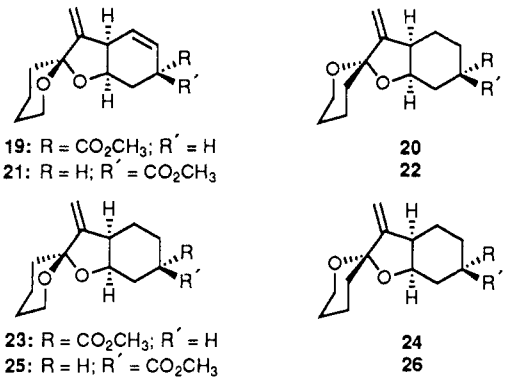
montmorillonite clay[13] (eq 4, 0.3 M, PhH, powdered 4-Å molecular sieves, 30 °C, 58–90%). Subjecting each isomer




to 5 mol % palladium acetate in the presence of either 10 mol % of triphenylarsine or of, preferably in this case, tri-*o*-tolylphosphine gave the full ring skeleton of $\Delta^1$-dehydrophyllanthocin (**19** and **20**,[6] 46%) and $\Delta^1$-dehydro-3-epiphyllanthocin (**21** and **22**,[6] 43%), respectively. The ratio of **19** to **20** (1.4:1.0) and of **20** to **21** (1.6:1.0) reflected the ratio of isomers epimeric at the anomeric center in the precursors **17** and **18**, respectively. No significance was attached to the stereochemistry at the anomeric center since previous studies[12] suggested this center would equilibrate to the natural configuration (vide infra).




In an ancillary study, we examined the reductive cyclization of **17** and **18**.[14] In contrast to the cycloisomerization, BBEDA proved to be the most effective ligand and polymethylhydrosiloxane (PMHS) the most effective silicon hydride. Exposing **17** and **18** independently to 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 6 mol % BBEDA, 1.5 equiv of acetic acid, and 10 equiv of PMHS in 1,2-dichloroethane at 30 °C for 1.5–2.0 h gave a 1:1.4 ratio of **23**:**24**[6] (from **17**) in 73% yield and a 1:1 ratio of **25**:**26**[6] (from **18**) in 86% yield.

Equilibration of the anomeric center of the isomeric pair **23**, **24** independently occurred smoothly with a catalytic amount of PPTS in PhH at 30 °C to give approximately the same 15:1 ratio. The assignment of the structure of the major isomer as **24** derives from spectral comparisons and the literature precedent.[12] Furthermore, MM2 calculations for **23**, **24** (R = R′ = H) predict that **24** is 1.7 kcal/mol more stable than **23**. The above ratio corresponds to 1.6 kcal/mol, a remarkable agreement. For comparison, the unsaturated analogues **19** and **20** were also equilibrated under identical conditions to a 6.5:1 ratio. The assignment of **20** as the major diastereomer derives from analogy to the saturated series and spectral comparisons.

The sensitivity of these oxygen substrates for palladium-catalyzed cycloisomerization may derive from difficulty in their ability to function as bidentate ligands toward palladium(+2). The C–O–C bond angle, which is in the forming ring, is larger than the corresponding angle in the all-carbon cases and may make such bis-coordination more difficult. The resulting slower rate of cyclization, combined with the sensitivity of the products toward decomposition by the catalysts, requires an appropriate ligand that permits reaction to proceed at lower temperatures, but at the same time tempers the catalyst to minimize product decomposition. For this series, the arsine ligand appears to offer the best compromise, although the other ligands we have employed also appear important for selective cases. The sequences **14** to **20** and **14** to **24** also constitute very facile constructions of the complete phyllanthocin ring system (three steps from readily available known starting materials) in a way that can permit easy analoging. In addition to the palladium-catalyzed cycloisomerization, this method for the synthesis of the very sensitive mixed glycosidic ketal[15] may be of more general use. The ready availability of the necessary cyclization substrates and the facility of the cycloisomerization should make this methodology broadly applicable to the construction of diverse tetrahydrofuryl-containing natural products.

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**Supplementary Material Available:** Spectral data for **4–13** and **17–26** (4 pages). Ordering information is given on any current masthead page.

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