On Pd-Catalyzed Cycloisomerization versus Cycloreduction. A General Strategy for Drimane Synthesis and a Short Total Synthesis of Siccanin

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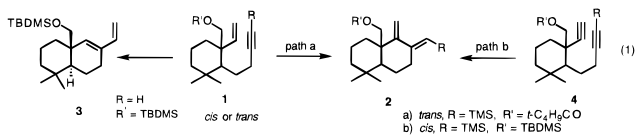
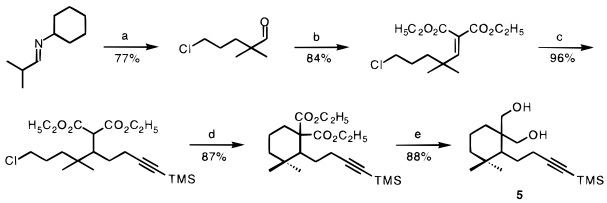
Our recently developed Pd-catalyzed cycloisomerization of enynes has offered an opportunity to develop novel synthetic strategies for complex targets.[1] The drimanes are an important terpenoid class whose members exert broad biological activities including antibacterial, antifungal, cytotoxic, insecticidal, etc.[2] To illustrate the types of new strategic insight proffered and to explore the scope of the cycloisomerizations illustrated in eq 1, path a, an effort directed at the evolution of a general approach to this family was undertaken. Under a wide variety of conditions, the *cis* isomer **1** (R = H or TMS) gave none of the cyclized product and the *trans* isomer gave only a 30% yield for R = H [2.5% $(dba)_3Pd_2$, 5% HOAc, 10% $(o\text{-}C_7H_7)_3P$, PhH, 80°]. In contradistinction to this result, an enyne metathesis to form **3**, which presumably involves similar intermediates, succeeds [5% TCPC^{TFE}, $(i\text{-}C_3H_7O)_3P$, PhH, 68% yield].[3] Clearly, the stereoelectronics of seemingly related processes are different. A possible source of the problem lies in the geometrical restrictions of a vinyl group in allowing intramolecular carbametalations. We, therefore, turned to consideration of a different new reaction being developed in our laboratories, the catalytic diyne reductive cyclization,[4] wherein its ability to form six-membered rings and its stereoelectronic requirements vis-a-vis the cycloisomerization would be compared.



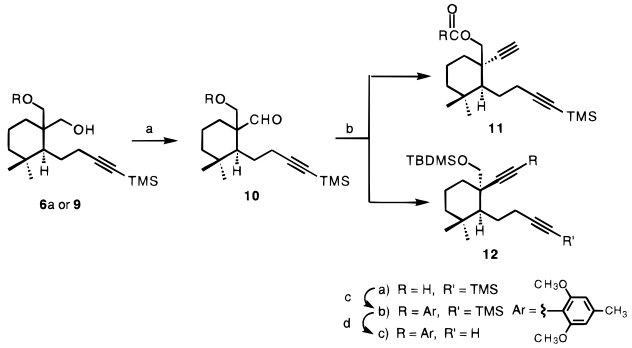
The synthesis of **4**, both *trans* and *cis*, requires differentiation of the hydroxy groups of the diol **5** prepared as shown in Scheme 1 in 48% overall yield. Surprisingly, acylation with either pivaloyl chloride or benzoyl chloride (C_5H_5N, CH_2Cl_2, rt) led to preferential reaction with the "more hindered" hydroxyl group with the latter giving better results. The monoester **6b**, isolated in 77% yield, easily and cleanly separates from the other products which are the diester **7b** (10%) and the alternate monoester (10%). Since the minor products can be converted back to **5**, a single recycle can boost the yield to 92%. On the other hand, silylation gives the monosilyl derivatives **8** and **9** in 40% and 58% isolated yields, respectively. Recycling the easily separated minor product **8** by acidic desilylation (TsOH, CH_3OH, rt, 96%) to **5** and silylation as before raises the yield of the desired silyl ether **9** to 80%. NOE experiments establish the chemoselectivity which is confirmed by the completed synthesis. Thus, **6** and **9** provide potential entry to either ring fusion series.

Scheme 1. Synthesis of Monocyclic Diol[a]

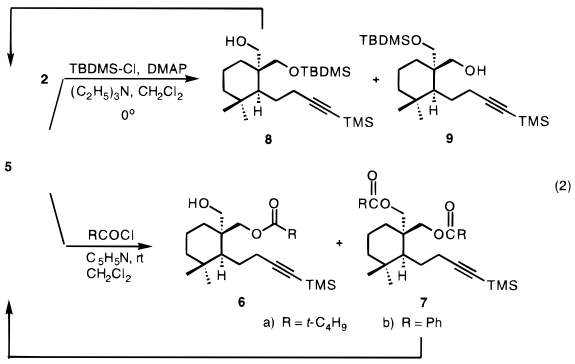


[a] (a) LDA, THF, $I(CH_2)_3Cl$, −78° to rt, workup with HCl, H_2O. (b) $CH_2(CO_2C_2H_5)_2$, $TiCl_4$, C_5H_5N, CCl_4, THF, 0°. (c) $TMSC{\equiv}CCH_2CH_2I$, $n\text{-}C_4H_9Li$, CuCN, ether, −78° to 0°. (d) 10% NaI, Cs_2CO_3, 3 Å MS, acetone, reflux. (e) LAH, THF, 0°.

Scheme 2. Synthesis of Diyne[a]



[a] (a) PCC, celite, CH_2Cl_2, from **6a** Q, from **9**, 92%. (b) $(CH_3O)_2P(O)CHN_2$, NaHMDS, THF, −78° to rt, 77% to **11**, 91% to **12a**. (c) (i) Morpholine, I_2, PhH, rt, (ii) Dimethyl orcinol, $n\text{-}C_4H_9Li$, THF, −78° to 0 °C, CuCN, 96%; (d) K_2CO_3, CH_3OH, rt, 97%.



Scheme 2 outlines the synthesis of the various diynes. Formation of the alkyne from the aldehyde failed with the Corey−Fuchs protocol.[5] Olefination via phosphonates[6] proved superior with excellent results obtained with dimethyl phosphonodiazomethane[6a,b] thereby providing the cyclization substrates **11** and **12a**. Subjection of **11** or **12a** to our reductive cyclization conditions [$(o\text{-}C_7H_7)_3P$, $(dba)_3Pd_2{\cdot}CHCl_3$, HOAc, $(C_2H_5)_3SiH$, PhH][4] failed. Among the various permutations explored, two variables proved important, ligand and acid. Use of poorer donor ligands like trifurylphosphine, Ph_3As, and Ph_3Sb led to some product **2a** but in low yields (eq 1). Switching from acetic acid to the slightly stronger acid, formic acid, presumably to help shift the equilibrium between the Pd(0) catalyst and the active hydridopalladium catalyst toward the latter, proved to be the major key. For example, *trans* diyne **11** cycloreduced to give **2a** in 87% yield [2.5% $(dba)_3Pd_2{\cdot}CHCl_3$, 10% Ph_3As, $(C_2H_5)_3SiH$, HCO_2H, $PhCH_3$, 80 °C, 20 min], but

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(2) Jansen, B. M. M.; de Groot, A. *Nat. Prod. Rep.* **1991**, *8*, 309. *Ibid.* **1991**, *8*, 319.

(3) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850.

(4) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. Also see Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491 in which six-membered rings form in a cycloisomerization of enediynes.

(5) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(6) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. Reich, H. J.; Willis, W. W. *J. Am. Chem. Soc.* **1980**, *102*, 5967. Comassetto, J.; Petragnani, N. *J. Organomet. Chem.* **1978**, *152*, 295. Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.

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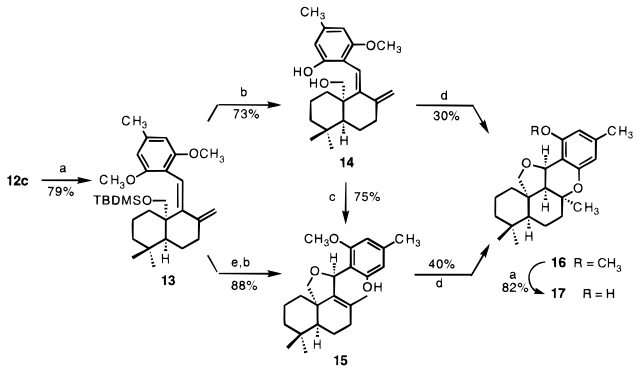
Scheme 3. A Synthesis of Siccanin[a]



[a] (a) 2.5% $(dba)_3Pd_2{\cdot}CHCl_3$, 10% trifurylphosphine, 2 equiv $(C_2H_5)_3SiH$, 2 equiv HCO_2H, $PhCH_3$, 80°. (b) NaH, C_2H_5SH, DMF, 100−120°. (c) $NaHSO_4$, acetone, 60°. (d) $BF_3{\cdot}$ether, CH_2Cl_2, ether, rt. (e) TsOH, CH_3OH, rt.

cis diyne gave **2b** in <15% yield. In the latter case, use of formic acid with *no* ligand proved much better, raising the yield to 98% under otherwise identical conditions.

With this new protocol, we targeted one of the most complex drimanes, siccanin (**17**, Scheme 3), a clinically important antifungal agent.[7] In spite of a number of efforts, only one synthesis was successful to date.[8,9] The effectiveness of a strategy emanating from this methodology may be compared to this successful route. Installation of the required aryl group by various permutations of the widely used Pd-catalyzed cross-coupling reaction failed.[10] On the other hand, the more classical Cu-catalyzed coupling,[11,12] as shown in Scheme 2, proceeded nearly quantitatively.

Cycloreduction of **12c** really tests the mettle of this new protocol because of the highly hindered nature of the product. Gratifyingly, the reductive cyclization saw no ill effects of the aryl substitution and provided **13** as a geometrically homogeneous crystalline diene in 79% isolated yield (see Scheme 3). Unambiguous creation of the alkene geometry sets the stage for the three remaining stereogenic centers, a critical benefit of the diyne cycloreduction. Attempts to directly cyclize **14** to siccanin methyl ether (**16**) with protonic acids normally lead to siccanochromene E methyl ether[9] and with sodium bisulfate to the tetrahydrofuran **15**. On the other hand, BF_3 etherate effects direct cyclization to siccanin methyl ether **16**.[13] Demethylation forms siccanin, identical spectroscopically in every respect (except optical rotation) with an authentic sample. This sequence requires 14 steps and proceeds in 3% overall yield.

Alternatively, cyclization of tetrahydrofuran **15** proceeds more satisfactorily to siccanin methyl ether (**16**) under the same conditions. The tetrahydrofuran **15** is preferably available from **13** by inverting the sequence, i.e., first protonic acid desilylation and initial cyclization followed by O-demethylation. The sequence via **15** requires 15 steps and proceeds in 5% overall yield.

The Pd-catalyzed reductive cyclization of diynes represents an attractive alternative to the Pd-catalyzed cycloisomerization to 1,3-dienes. By minimization of steric constraints, cyclizations that fail in the latter case may now succeed. For the cycloreduction, a more general protocol in which formic acid is the key has now emerged. In the first test of this reductive cyclization to solve a problem of complex synthesis, the reaction performed exceptionally well. The dialkylidenecycloalkanes that result have great versatility, especially with respect to the type of functionality commonly found in the drimanes. Both the *cis* and *trans* ring fused drimanes might be available. Furthermore, asymmetric syntheses also should be readily available using the protocol of Mukaiyama, who has developed an oxazepandione as a chiral version of the alkylidenemalonate for cuprate additions.[14] Further work to explore the generality of this strategy for the syntheses of other biologically interesting drimanes will be the focus of future efforts.

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Supporting Information Available: Characterization data for ethyl 2-ethoxycarbonyl-3-(4-trimethylsilyl-3-butynyl)-4,4-dimethyl-7-chloroheptanoate, 1,1-bis(ethoxycarbonyl)-2-(4-trimethylsilyl-3-butynyl)-3,3-dimethylcyclohexane, **5**, **9**, and **12**−**17** and experimental procedure for cyclization of **12c** to **13** (5 pages). Ordering information is given on any current masthead page.

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