

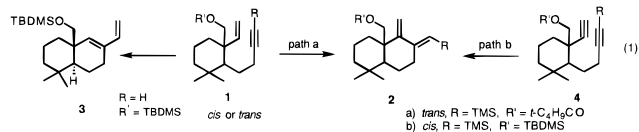
On Pd-Catalyzed Cycloisomerization versus Cycloreduction. A General Strategy for Drimane Synthesis and a Short Total Synthesis of Siccanin

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Received December 28, 1995

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)₃Pd₂, 5% HOAc, 10% (*o*-C₇H₇)₃P, PhH, 80°]. In contradistinction to this result, an enyne metathesis to form **3**, which presumably involves similar intermediates, succeeds [5% TCPC^{TFE}, (*i*-C₃H₇O)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 (C₅H₅N, CH₂Cl₂, 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, CH₃OH, 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.

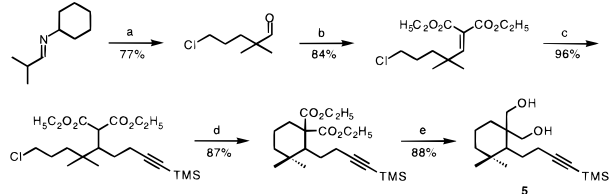
(1) Trost, B. M.; Krusche, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 233. Trost, B. M.; Phan, L. T. *Tetrahedron Lett.* **1993**, *34*, 4735. Trost, B. M.; Tasker, A. S.; Rühter, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670.

(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.

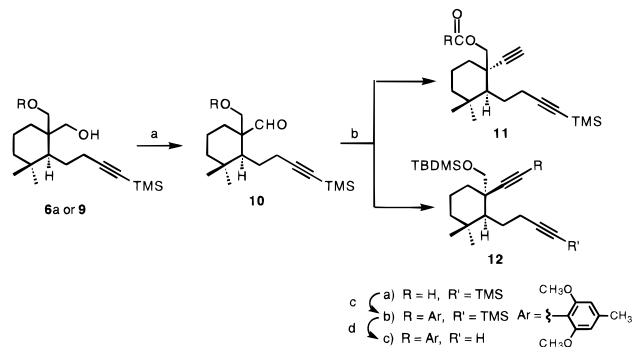
(4) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. Also see Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491 in which six-membered rings form in a cycloisomerization of enediynes.

Scheme 1. Synthesis of Monocyclic Diol^a

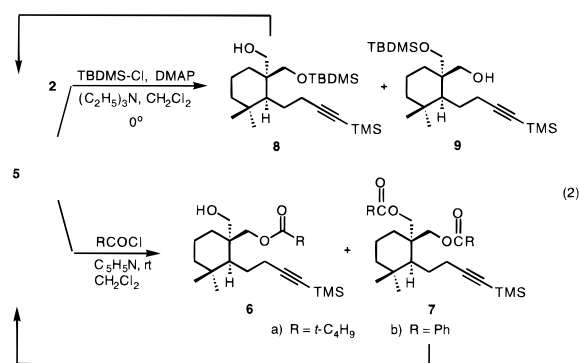


^a (a) LDA, THF, I(CH₂)₃Cl, -78° to rt, workup with HCl, H₂O. (b) CH₂(CO₂C₂H₅)₂, TiCl₄, C₅H₅N, CCl₄, THF, 0°. (c) TMSC≡CCH₂CH₂I, *n*-C₄H₉Li, CuCN, ether, -78° to 0°. (d) 10% NaI, Cs₂CO₃, 3 Å MS, acetone, reflux. (e) LAH, THF, 0°.

Scheme 2. Synthesis of Diyne^a



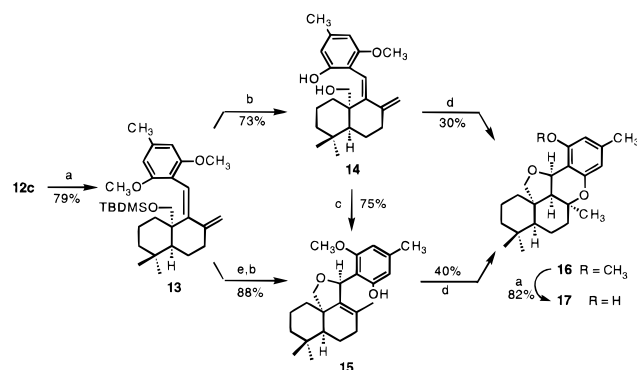
^a (a) PCC, celite, CH₂Cl₂, from **6a** Q, from **9**, 92%. (b) (CH₃O)₂P(O)CHN₂, NaHMDs, THF, -78° to rt, 77% to **11**, 91% to **12a**. (c) (i) Morpholine, I₂, PhH, rt, (ii) Dimethyl orcinol, *n*-C₄H₉Li, THF, -78° to 0 °C, CuCN, 96%; (d) K₂CO₃, CH₃OH, rt, 97%.



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 phosphonates⁶ 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*-C₇H₇)₃P, (dba)₃Pd₂·CHCl₃, HOAc, (C₂H₅)₃SiH, PhH]⁴ failed. Among the various permutations explored, two variables proved important, ligand and acid. Use of poorer donor ligands like trifurylphosphine, Ph₃As, and Ph₃Sb 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)₃Pd₂·CHCl₃, 10% Ph₃As, (C₂H₅)₃SiH, HCO₂H, PhCH₃, 80 °C, 20 min], but

(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.; Petragani, N. *J. Organomet. Chem.* **1978**, *152*, 295. Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.

Scheme 3. A Synthesis of Siccanin^a

^a (a) 2.5% (dba)₃Pd $\cdot$ CHCl₃, 10% trifurylphosphine, 2 equiv (C₂H₅)₃SiH, 2 equiv HCO₂H, PhCH₃, 80°. (b) NaH, C₂H₅SH, DMF, 100–120°. (c) NaHSO₄, acetone, 60°. (d) BF₃ $\cdot$ ether, CH₂Cl₂, ether, rt. (e) TsOH, CH₃OH, 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.

(7) (a) Ishibashi, K. *J. Antibiot., Ser. A* **1962**, *15*, 161. (b) Ishibashi, K.; Hirai, K.; Arai, M.; Sugawara, S.; Endo, A.; Yasuma, A.; Matsuda, H.; Muramatsu, T. *Ann. Sankyo Res. Lab.* **1970**, *22*, 1. (c) Bellotti, M. G.; Riviera, L. *Chimioterapia* **1985**, *4*, 431. (d) Hirai, K.; Nozoe, S.; Tsuda, K.; Iitake, Y.; Shirasawa, M. *Tetrahedron Lett.* **1967**, 2177. (e) Hirai, K.; Suzuki, K. T.; Nozoe, S. *Tetrahedron* **1971**, *27*, 6057. (f) Sugawara, S. *Antimicrob. Agents Chemother.* **1969**, 253. (g) Arai, M.; Ishibashi, K.; Okazaki, H. *Antimicrob. Agents Chemther.* **1969**, 247. (h) Crippa, D.; Albanese, C. G.; Sala, G. P. *G. Ital. Dermatol. Venereol.* **1985**, *120*, LVII and references therein. Also, see: Kitano, N.; Kondo, F.; Kusano, K.; Ishibashi, K. German Patent 2458886; *Chem. Abstr.* **1975**, *83*, 197813. Kondo, K.; Nakada, S. Japanese Patent 02204413; *Chem. Abstr.* **1991**, *114*, 30165. Wood, L.; Calton, G. J. U.S. Patent 5260066; *Chem. Abstr.* **1994**, *120*, 200438.

(8) For some synthetic efforts, see: Nozoe, S.; Hirai, K. *Tetrahedron* **1971**, *27*, 6073. Oida, S.; Ohashi, Y.; Yoshida, A.; Ohki, E. *Chem. Pharm. Bull.* **1972**, *20*, 2634. Yoshida, A.; Oida, S.; Ohashi, Y.; Tamura, C.; Ohki, E. *Chem. Pharm. Bull.* **1972**, *20*, 2642. Oida, S.; Ohashi, Y.; Ohki, E. *Chem. Pharm. Bull.* **1973**, *21*, 528. Liu, H.; Ramani, B. *Tetrahedron Lett.* **1988**, *29*, 6721. Kato, M.; Matsumura, Y.; Heima, K.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1991.

(9) For a successful synthesis, see: Kato, M.; Heima, K.; Matsuma, Y.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1981**, *103*, 2434. Kato, M.; Matsuma, Y.; Heima, K.; Fukamiya, N.; Kabuto, C.; Yoshikoshi, A. *Tetrahedron* **1987**, *43*, 711.

(10) Cf: Hirthhammer, M.; Volhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2481. Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. Dieck, H. A.; Heck, R. F. *Ibid.* **1975**, *93*, 259. Sanogashire, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(11) Oliver, R.; Walton, D. R. M. *Tetrahedron Lett.* **1972**, 5209. Verboom, W.; Westmijze, H.; Bos, H. J. T. *Tetrahedron Lett.* **1978**, 1441. Letyn, J. M.; Spronck, H. J. W.; Salemink, C. A. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 187.

(12) For iodination of the alkyne, see: Kayama, M. *J. Med. Chem.* **1987**, *30*, 552. Southwick, P. L.; Kirchner, J. R. *J. Org. Chem.* **1962**, *27*, 3305.

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 ether⁹ and with sodium bisulfate to the tetrahydrofuran **15**. On the other hand, BF₃ 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.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences Institute, and the National Science Foundation for their generous support of our programs. F.J.F. held a NSF predoctoral fellowship for part of his stay, and W.J.W. held a NATO postdoctoral fellowship administered by the SERC of the United Kingdom. Mass spectra were provided by the Mass Spectrometry Facility at the University of California—San Francisco. We are indebted to Johnson Matthey Alfa Aesar for their generous loan of palladium salts and to Professor Michiharu Kato of Tohoku University for a generous gift of natural siccanin.

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.

JA9543098

(13) Partial ¹H NMR data have been recorded for siccanin methyl ether; see ref 7e. Our data do not agree. Our spectral data are in full accord with the assignment. Moreover, the successful completion of our synthesis and a direct comparison of our synthetic siccanin with an authentic sample confirm the correctness of our assignment.

(14) Mukaiyama, T.; Takida, T.; Fumimoto, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3368.