Facile, Palladium(II)-Mediated Synthesis of Bridged and Spirocyclic Bicycloalkenones

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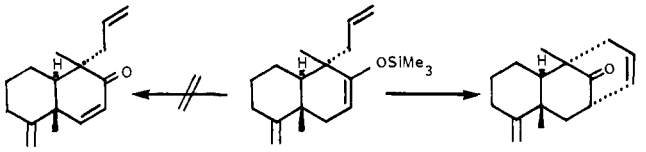
The reaction of silyl enol ethers with $Pd(OAc)_2$ in CH_3CN has been shown by Ito et al. to be a valuable route to α,β-unsaturated carbonyl compounds.[1] During our application of this procedure to the ajugarin precursor **2**,[2] we isolated, instead of the expected enone **1**, a single unconjugated $C_{16}H_{22}O$ ketone, mp 89–90 °C, in 80% yield. Detailed analytical and spectroscopic characterization, including 400-MHz ^1H NMR spectrometry with decoupling,[3] demonstrated this product to be the bridged tricyclic dienone **3**.

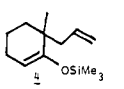
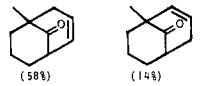
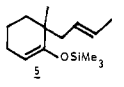
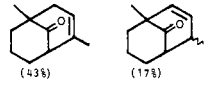
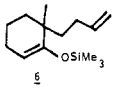
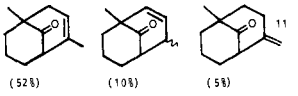
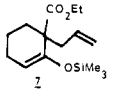
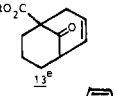
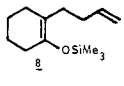
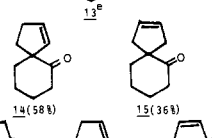
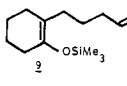
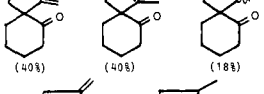
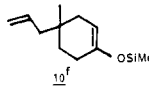
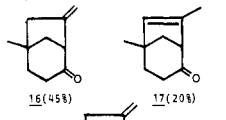
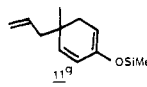
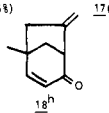
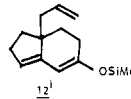
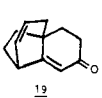


1 2 3

Previous work by the Kyoto group has shown that formation of simple cycloalkenones can occur by cyclization of ω-vinyl silyl enol ethers that are structurally precluded from dehydrosilylation to conjugated enones.[4] Our facile cyclization, in successful competition with the formation of the alternative product **1**, suggested that such $Pd(OAc)_2$-mediated cyclizations might serve as favored routes to bridged and spirocyclic bicycloalkenones *even when competing conjugated enone formation is structurally possible*. We now report preliminary studies that support this assumption and demonstrate unexpected regiospecificity for some of these novel ring closures.

A variety of cyclopentanones and cyclohexanones bearing unsaturated side chains α or γ to the carbonyl group were converted to trimethylsilyl enol ethers and these were subjected to reaction with $Pd(OAc)_2$ under standard conditions (Table I). The thermodynamic Me_3Si enol ethers were generated from the ketones by the $HN(SiMe_3)_2$–$(CH_3)_3SiI$ method of Miller and McKean,[5] while the kinetic Me_3Si enol ethers were prepared by using LDA and Me_3SiCl according to House.[6] A solution of Me_3Si enol ether (1.2 mmol) in 2.0 mL of dry 1:1 CH_3CN–CH_2Cl_2 was added dropwise to a solution of $Pd(OAc)_2$ (Aldrich, 1.2 mmol)[7] in 10 mL of freshly distilled CH_3CN. The resulting brown suspension was stirred under N_2 at 25 °C for 1–15 h, with TLC monitoring (Si gel, 20:1 hexane–EtOAc) for disappearance of starting material. Upon completion, the reaction was gently evaporated to dryness at reduced pressure, the residue taken up in 10 mL of hexane, and Pd metal removed by filtration through Celite. The filtrate was washed with ice cold 1 N HCl and then aqueous $NaHCO_3$, dried, and gently evaporated at reduced pressure to yield the products reported below. Cyclization products were separated from byproducts by flash chromatography (Si gel, 40:1 hexane–EtOAc). However, the regioisomeric olefins formed in some of the cyclizations were characterized as isomer mixtures

Table I. Cyclizations of Alkenyl Me_3Si Enol Ethers Using $Pd(OAc)_2$

Silyl Ethers	Cyclization Products (Yields)	Time (hrs)	Yield[a]
 4	 (58%) (14%)	2	72%[b]
 5	 (43%) (17%)	36	60%[c,d]
 6	 (52%) (10%) (5%)	11	67%[d]
 7	 13[e]	24	47%[c]
 8	 14(58%) 15(36%)	3	85%
 9	 (40%) (40%) (18%)	3	98%
 10[f]	 16(45%) 17(20%)	5	65%
 11[g]	 18[h]	5	68%
 12[i]	 19	1	42%[j]

[a] The yield refers to cyclization product or cyclization product mixture after purification by chromatography (see text). [b] Ca. 15–17% of uncyclized conjugated enone was formed. [c] Ca. 7% of uncyclized conjugated enone was formed. [d] The major cyclization product had spectroscopic properties and gave a 2,4-dinitrophenylhydrazone derivative identical with that reported by Marshall (Marshall, J. A.; Schaeffer, D. J. *J. Org. Chem.* 1965, *30*, 3642) (found for 2,4-DNP: C, 59.06; H, 5.82). [e] Bicyclononenone 13, mp 42–44 °C (lit. mp 45 °C), had spectroscopic properties as described by: Colvin, E. W.; Parker, W. *J. Chem. Soc.* 1965, 5764 (found for 13: C, 69.17; H, 7.88). [f] The cyclohexanone precursor of 10 was prepared by allylation of the kinetic enolate of 6-methyl-3-ethoxy-2-cyclohexenone, reduction with *i*-Bu_2AlH, and then Birch reduction of the resulting enone; cf.: Stork, G.; Danheiser, R. *J. Org. Chem.* 1973, *38*, 1775. [g] The cyclohexenone precursor of 11 was prepared by the procedure of reference *f*, without the Birch reduction step. For an alternative synthesis, see: Vittorrelli, P.; Peter-Katalinic, J.; Mukherjee-Muller, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* 1975, *58*, 1379. [h] Compound 18: IR ν_{CO} 1680, 1415, 890 cm^{-1}; ^1H NMR δ 6.93 (1 H, dd, J = 10, 2 Hz), 5.77 (1 H, dd, J = 10, 2 Hz), 5.25 (1 H, br s), 5.03 (1 H, br s), 3.44 (1 H, br d, J = 5 Hz), 2.38 (2 H, m), 2.07 (1 H, d, J = 11 Hz), 1.79 (1 H, ddd, J = 11, 5, 2 Hz), 1.36 (3 H s); UV (CH_3OH) λ_{max} 230 nm, ϵ 7000. [i] Compound 12 was prepared from 9-allylhydrindenone, synthesized by the procedure of Caine et al. (Caine, D.; Alejande, A. M.; Ming, K.; Powers, W. *J. Org. Chem.* 1972, *37*, 706) using $HN(SiMe_3)_2$–Me_3SiI. [j] Ca. 21% of the uncyclized linear-conjugated dienone was formed.

(1) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(2) Kende, A. S.; Roth, B.; Kubo, I. *Tetrahedron Lett.*, in press.

(3) ^1H NMR of **3**: δ 5.83 (1 H, ddt, J = 10, 6, 2 Hz), 5.46 (1 H, ddt, J = 10, 5, 2, 1 Hz), 4.66 (1 H, s), 4.60 (1 H, s), 2.96 (1 H, ddd, J = 10, 6, 1 Hz), 2.45 (1 H, dd, J = 18, 5 Hz), 2.38 (1 H, dd, J = 13, 4 Hz), 2.31 (1 H, d, J = 14 Hz), 2.19 (2 H, m), 2.09 (1 H, dd, J = 14, 10 Hz), 1.86 (1 H, m), 1.63 (1 H, m), 1.54 (1 H, m), 1.25 (2 H, m), 1.08 (3 H, s), 0.93 (3 H, s). Found for **3**: C, 83.31; H, 9.63.

(4) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494. Ito, Y.; Aoyama, H.; Saegusa, T. *Ibid.* **1980**, *102*, 4519.

(5) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.

(6) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(7) The use of $PdCl_2$ in CH_3CN upon substrate **4** gave a 2:1 ratio of enone to bicyclic product, rather than the 4:1 inverse ratio observed for $Pd(OAc)_2$. We have not been successful to date in achieving these cyclizations using catalytic $Pd(OAc)_2$ and benzoquinone or $Cu(OAc)_2$–O_2 as oxidants.

(8) These reactions do not appear to proceed through formation of π-allylpalladium(II) complexes involving the alkenyl side chain (cf. **11**→**18**). Acceptable mechanisms include the initial formation of oxo (π-allyl)palladium(II) complexes (as proposed in ref 4) or initial coordination of the alkenyl side chain to Pd(II) followed by nucleophilic attack with the enol ether double bond (cf.: Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973). Experiments to distinguish these possibilities are in progress.

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because of difficulty in their quantitative separation by TLC or GC. All product ratios and structures were established by 400-MHz ^{1}H NMR spectrometry with decoupling; all pure compounds as well as regioisomer mixtures were further characterized by mass spectrometric analyses and infrared spectra. Control experiments involving the substrate **4** showed very similar isomer ratios at 2 h vs. 20 h of reaction time. The yields in Table I refer to isolated yields after chromatography. They are not optimized, and some product loss from volatility may have occurred.

The data of Table I reveal this cyclization to be a powerful and often regioselective method, with some specific limitations. It appears that in the cyclohexene series a second substituent (e.g., CH_3 or COOR) on the carbon bearing the alkenyl chain is essential for cyclization to compete with conjugated enone formation. Thus, in contrast to the smooth cyclization of **4**, the substrate 3-allyl-2-(trimethylsiloxy)cyclohexene with $Pd(OAc)_2$ under our conditions gave a mixture of conjugated enone and starting ketone, but no bicyclic product. The reason for this may be conformational: an axial side chain is required to form the new bridge. It is also noteworthy that for those cases where a new six-membered ring bridge is generated, the double bond in the new bridge forms predominantly away from the more highly substituted bridgehead carbon.

Compounds **8** and **9** in Table I show that excellent yields of spirobicycloalkenones can be obtained by cyclization of suitable precursors. In the case of the Me_3Si enol ether **8**, the structures of the spirocyclic enones **14** and **15** formed as a 3:2 mixture were confirmed by the following stereoconvergent transformations: (a) catalytic reduction of the mixture H_2, Pd–C, and EtOAc at 1 atm and 25 °C to give exclusively the known spiro[4.5]decan-6-one;[9] (b) hydroboration–oxidation (10 equiv of BH_3–THF, in THF, 0 °C; then made alkaline with H_2O_2 followed by PCC oxidation) to give 70% of spiro[4.5]decane-2,6-dione, mp 47–48 °C (hexane).[10]

When an allyl substituent is γ to the trimethylsiloxy carbon, the $Pd(OAc)_2$ closure leads to *bridged five-membered rings* (compounds **10** and **11**). In the simplest case of **10**, the cyclization gives in 65% yield a 2:1 ratio of the exocyclic and endocyclic olefins **16** and **17**. For the Me_3Si dienol ether **11** only the exocyclic olefin **18** is observed, possibly reflecting the higher strain energy of the endocyclic olefin in this system.

An intriguing example of the regiospecificity of the reaction is the cyclization of the Me_3Si dienol ether **12**. The sole cyclization product is a conjugated enone (IR ν_{CO} 1680 cm^{-1}; UV λ_{max} (MeOH) 234 nm, ϵ 11 600) which can be shown by mass and 400-MHz ^{1}H NMR spectroscopy to have the structure **19**.[11] Here a new six-membered ring bridges the allyl terminus to the γ position of the original conjugated enone system.

Although the full scope and mechanism of these novel cyclizations remain to be defined, it is already evident that these simple reactions offer potential entry to a variety of bridged and spirocyclic systems. Applications of this methodology to the synthesis of phyllocladene,[12] quadrone,[13] and other polycyclic natural products are in progress.

Acknowledgment. Partial support of this work by Grant CA-18846, awarded by the National Cancer Institute (USPHS) is gratefully acknowledged. We are indebted to Jen Chen and Pawel Fludzinski for the synthesis of several of the ketone precursors to the Me_3Si enol ether substrates in Table I.

Registry No. 4, 80953-94-2; **5**, 80953-95-3; **6**, 80953-96-4; **7**, 80953-97-5; **8**, 80953-98-6; **9**, 80953-99-7; **10**, 80954-00-3; **11**, 80954-01-4; **12**, 80954-02-5; **13**, 4696-33-7; **14**, 61765-59-1; **15**, 14054-26-3; **16**, 80954-03-6; **17**, 80954-04-7; **18**, 80954-05-8; **19**, 80954-06-9; 1-methyl-9-oxobicyclo[3.3.1]non-3-ene, 80954-07-0; 1-methyl-9-oxobicyclo[3.3.1]non-3-ene, 80954-08-1; 1,4-dimethyl-9-oxobicyclo[3.3.1]non-3-ene, 4071-70-9; 1,4-dimethyl-9-oxobicyclo[3.3.1]non-3-ene, 80954-09-2; 1-methyl-4-methylene-9-oxobicyclo[3.3.1]nonane, 80954-10-5; 4-methylenespiro[4.5]decan-6-one, 42988-49-8; 4-methylspiro[4.5]dec-3-ene-6-one, 61765-60-4; 4-methylspiro[4.5]dec-2-ene-6-one, 80954-11-6; $Pd(OAc)_2$, 3375-31-3.

(9) Hart, H.; Leiner, L. R. *J. Org. Chem.* **1967**, *32*, 2669. Quadrat-i-Khuda, M.; Ray, A. S. *J. Indian Chem. Soc.* **1939**, *16*, 525. Our semicarbazone, mp 187–189 °C (lit. mp 187–190 °C, 188–190 °C), contained 62.94% C and 9.07% H.

(10) Spiro[4.5]decane-2,6-dione: IR ν_{CO} 1775, 1715 cm^{-1}; ^{1}H NMR δ 2.80 (1 H, d, J = 18 Hz), 2.57–2.24 (4 H, m), 2.01 (1 H, d, J = 18 Hz), 1.96–1.58 (8 H, m). For a related spirodiketone, see: Ganter, C.; Warszawski, R.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1963**, *46*, 320.

(11) Compound **19**: ^{1}H NMR ($CDCl_3$) δ 5.90 (1 H, ddd, J = 9, 6, 2 Hz), 5.79 (1 H, s), 5.54 (m, 1 H), 2.98 (1 H, dd, J = 7.5, 6 Hz), 2.86 (1 H, dd, J = 15, 2 Hz), 2.15 (1 H, dd, J = 15, 4 Hz), 2.52–2.42 (2 H, m), 2.09–1.62 (6 H, m).

(12) Briggs, L. H.; Cain, B. F.; Cambie, R. C.; Davis, B. R. *J. Chem. Soc.* **1962**, 1840 and references cited therein.

(13) Rainieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499.

Biogenetic-Type Total Synthesis of (±)-Triptonide and (±)-Triptolide

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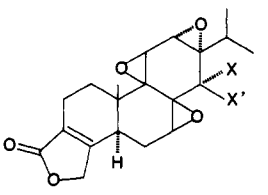
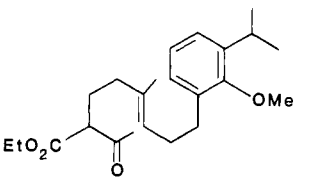
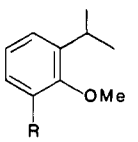
Triptolide (**1**) and triptonide (**2**), potent cytotoxic agents occurring in *Tripterygium wilfordii* Hook F,[1] have been the objectives of considerable synthetic effort during recent years.[2-4] In a departure from previous approaches, we have carried out an abbreviated, facile biogenetic-type total synthesis, featuring cyclization of a geranylgeraniol surrogate (**3**), in which a β-keto ester initiator serves as a covenient precursor of the unsaturated lactone unit and an appropriately substituted benzenoid unit acts not only as a terminator but also constitutes the framework for the polyepoxide moiety of the natural product system.



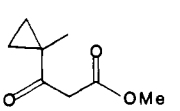
1 X=H; X'=OH
2 X,X'=O



3



4 R=H
5 R=CH_2OH
6 R=CH_2Br



7

2-Isopropylanisole (**4**) (obtained in 90% yield by alkylation of 2-isopropylphenol with NaH/MeI in THF at room temperature) was *o*-metalated with *n*-BuLi in TMEDA at room temperature, after which reaction with formaldehyde (generated from paraformaldehyde at 140 °C) gave rise to benzylic alcohol **5** (60% from **4**).[5] The corresponding bromide (**6**) (produced in 90% yield

(1) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7194.

(2) Buckanin, R. S.; Chen, S. J.; Frieze, D. M.; Sher, F. T.; Berchtold, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 1200 and preceding publications.

(3) Koike, H.; Tokoroyama, T. *Chem. Lett.* **1979**, 333; *Tetrahedron Lett.* **1978**, 4531.

(4) (a) van Tamelen, E. E.; Demers, J. P.; Taylor, E. G.; Koller, K. *J. Am. Chem. Soc.* **1980**, *102*, 5424 and preceding publications. (b) Garver, L. C.; van Tamelen, E. E. *Ibid.* **1982**, *104*, 867.

(5) **5**: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 6 H, J = 6.9 Hz, $CHMe_2$), 2.25 (br t, 1 H, J = 5.4 Hz, O*H*), 3.37 (sept, 1 H, J = 6.9 Hz, $CHMe_2$), 3.79 (s, 3 H, OCH_3), 4.72 (br d, 2 H, J = 5.4 Hz, CH_2O), 7.11–7.32 (m, 3 H, aromatic H).

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