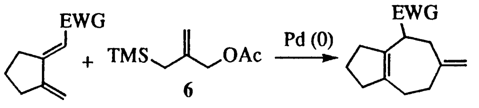
CHEMISTRY LETTERS, pp. 2245-2248 1994. © 1994 The Chemical Society of Japan

Pd-Catalyzed Cycloaddition of Vinylcyclopentenes with Trimethylenemethane. Substituent Effect on [4+3] *vs* [3+2] Selectivity

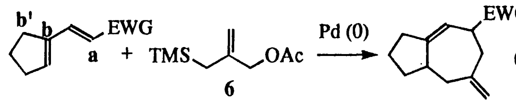
Barry M. TROST* and Shoko YAMAZAKI†
Department of Chemistry, Stanford University, Stanford, California 94305-5080, U.S.A.

The Pd-catalyzed reaction of 2-vinylcyclopentenes **2** and **3** with trimethylenemethane gave [4+3] and [3+2] cycloadducts. Derivatization of 2-vinylcyclopentenones with bulky ketal substituents served to enhance seven-membered ring formation.

Construction of seven-membered rings is an important challenge since they are found in a wide range of natural products, including, for example, hydroazulene frameworks.1) Compared to five- and six-membered rings, general methods for seven-membered ring synthesis are relatively few.2) A [4+3] cycloaddition reaction conceptually is an efficient synthetic method for formation of seven-membered rings.3) Recently, we reported that Pd-catalyzed [4+3] cycloadditions of trimethylenemethane (TMM) leads to hydroazulene derivatives.4) The approach involves a 1,2-dimethylene cyclopentane, which is restricted to the cisoid conformation, as a C_4 diene partner (eq 1). The generalization of this strategy depends upon its extention to conformationally more mobile dienes. As part of our efforts to further develop and extend this Pd-catalyzed [4+3] cycloaddition methodology, we have investigated the possibility of a [4+3] cycloaddition of the type shown in eq 2.

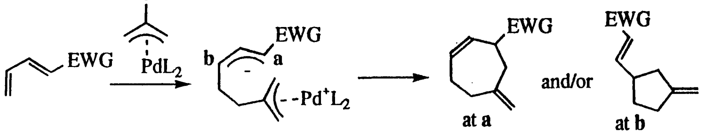


(eq 1)



(eq 2)

Compared to the 1,2-dimethylenecyclopentane, the vinylcyclopentene may prefer [3+2] cycloaddition rather than [4+3] cycloaddition since the diene part is not restricted to a cisoid conformation. For example, Pd-catalyzed reaction of dimethyl (*E*, *E*)-muconate with TMM gave a 1 : 1.1 mixture of seven- and five-membered rings,5) while the 1,2-dimethylenecyclopentanes gave ratios of 2.4 : 1 to 36 : 1 for seven- and five-membered rings respectively.4) However, considering the proposed stepwise mechanism of the cycloaddition,4,6) introduction of a bulky group at position **b** may enhance [4+3] selectivity (eq 3). In this report, we have examined the effects of carbonyl, ketals, and silicon-protected alcohol substituents at **b**'-position of a vinylcyclopentene on [4+3] *vs* [3+2] selectivity (eq 2).



(eq 3)

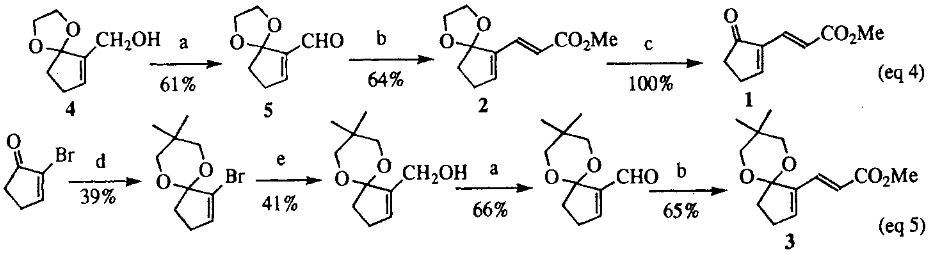
The cyclopentenenone **1** and its derivatives **2**, **3** and **13** were chosen because of their synthetic versatility for further elaboration of functional groups to natural products. Sterically hindered ketal and bulky silicon-

---

† Present address: Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630.

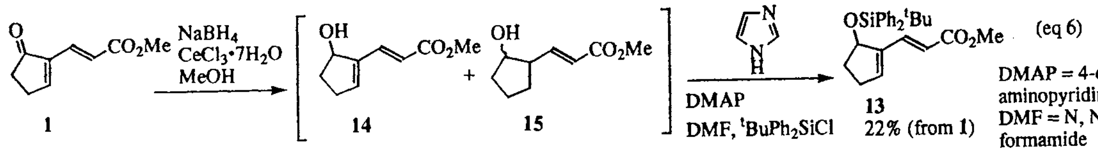
protected alcohol groups are expected to favor a cisoid conformation in the diene substrates. In addition to the steric effects, the electronic effect of a carbonyl group and its derivatives on [4+3] *vs* [3+2] selectivity are also of interest.

The preparation of substrates **1**-**3** and **13** was carried out according to the following scheme. The ethylene glycol ketal **4**, which is readily available according to the literature procedure,7) was oxidized with chromium trioxide-pyridine in methylene chloride to give 2-formylcyclopentenone ethylene ketal **5**8) in 61% yield. The reaction of **5** and trimethylphosphonoacetate in the presence of lithium chloride and DBU gave methyl ester **2**8) in 64% yield. Treatment of **2** with oxalic acid in methylene chloride - water gave **1**8) quantitatively (eq 4). Direct conversion of **1** to sterically hindered ketal **3** with 2,2-dimethylpropan-1,3-diol was unsuccessful. Therefore, **3**8) was prepared by the same procedure as for **2** (eq 5).



a: CrO_3-$(C_5H_5N)_2$/CH_2Cl_2,
b: $(MeO)_2POCH_2CO_2Me$/ LiCl/DBU/CH_3CN,
c: $(COOH)_2$/CH_2Cl_2/H_2O,
d: $HOCH_2CMe_2CH_2OH$/ pTsOH/benzene,
e: i) n-BuLi, ii) $(HCHO)_n$

Silicon-protected alcohol **13** was prepared as follows (eq 6). Reduction of **1** with sodium borohydride-cerium chloride gave a mixture of products, consisting of the desired alcohol **14**, the 1,4-reduced dihydro compound **15**, and another impurity (NMR analysis). Column chromatography failed to give the alcohol **14** in pure form. After treatment of the crude mixture with t-butyldiphenylchlorosilane, a 22% yield from **1** of desired compound **13**8) could be separated after column chromatography.



DMAP = 4-dimethylaminopyridine
DMF = N, N-dimethylformamide

For the cycloaddition reactions of **1**-**3** and **13**,9,10) the dienes and TMM precursor **6** or **7** were subjected to 5 mol% of a Pd(0) catalyst pre-generated by treating 5 mol% palladium acetate with 35 mol% triisopropyl phosphite (12.5 mol% 1,3-bis(diphenylphosphino)propane in entry 5) and 10 mol% of butyl lithium at room temperature. The results are listed in Table 1. Cycloaddition of **1** with **6** (1 equiv) in THF (60 °C, 1.5 h) gave only the five-membered ring cycloadduct **8**8) in 69% yield (entry 1). While the initial addition occurred as required for [4+3] cycloaddition, the regioselectivity of the second step reflects the normal kinetic preference for five to seven membered ring formation. Reaction of **2** with **6** (1 equiv) in THF (60 °C, overnight) gave mainly recovered starting ketal **2** and trace amounts of a mixture of seven- and five-membered products **9** and **10** (entry 2). Reaction of **2** with **6** (2 equiv) in toluene (110 °C, 6 days) gave a mixture of seven- and five-membered compounds **9** and **10** in 56% yield, accompanied by recovered **2** (19%) (entry 3). The ratio of seven- and five-membered ring products was 1 : 1.5. Better product yield was obtained by using an excess amount of the TMM precursor **7**. Thus, reaction of **2** and **7** (4 equiv) in THF (60 °C, overnight) gave **9**8) and **10**8) easily separated by column chromatography in 87% yield (**9** : **10** = 1 : 1.2) (entry 4). Cycloaddition of ketal **3** with **7** (2 equiv) in THF (60 °C, 6 h) gave a mixture of **11**8,11) and **12**8,12) also separable by column chromatography in 81% yield (entry 7). The ratio of seven- and five-membered ring products was 1.5 : 1. Thus, the more sterically hindered ketal **3** favors the seven-membered ring. However, in the presence of an excess amount of

TMM precursor **7**, longer reaction times reduce the yield of **11**, probably because further reaction occurs (entry 8, see also entry 6). By NMR analysis, both **9** and **11** were >9:1 single diastereoisomers.

Crude NMR of the cycloaddition reaction mixture of **13** with TMM-PdL$_2$ shows that the mixture possibly contained both five- and seven-membered ring cycloadducts (entry 10). In addition, diastereomers of each were present. However, these products could not be purified by column chromatography or preparative GC. Only a 7% yield of the five-membered ring adduct **16** (single diastereomer)[8)] was isolated.

The structure of the seven- and five-membered cycloadducts were assigned as follows. ^{1}H NMR spectra of **9** and **11** show one olefinic proton (δ 6.20 for **9**, δ 6.45 for **11**) in addition to two exocyclic methylene protons at δ 4.79-4.83. The protons α to the ester appear at δ 3.15 for **9** and δ 3.12 for **12**. The carbonyl frequencies for the saturated esters appear at 1735 cm^{-1} for **9** and 1730 cm^{-1} for **11**. On the other hand, ^{1}H NMR spectra of **8**, **10**, **12** and **16** show two doublets corresponding to olefinic protons coupled to each other (δ 5.85, 6.96, J = 16 Hz for **8**, δ 5.82, 7.23, J = 16 Hz for **10**, δ 5.79, 7.46, J = 16 Hz for **12**, δ 5.71, 6.89, J = 15.8 Hz for **16**) in addition to two exocyclic methylene protons at δ 4.84-4.91. The carbonyl frequencies of **8**, **10**, **12** and **16** for the unsaturated esters appear at 1702-1720 cm^{-1}. The ^{1}H NMR spectra of **9** and **11** also exclude the possibility of the alternate [3+2] cycloadducts (β-attack products) **17**; the chemical shifts of the exo methylene protons are characteristic of a seven-membered ring and the protons α to the ester are in the region of the seven-membered allylic ester obtained previously (δ 3.1-3.4).[4,5)] Compound **18** for comparison shows δ 4.92 for exo methylenes and δ 3.02 for the α proton of the non-allylic saturated ester.

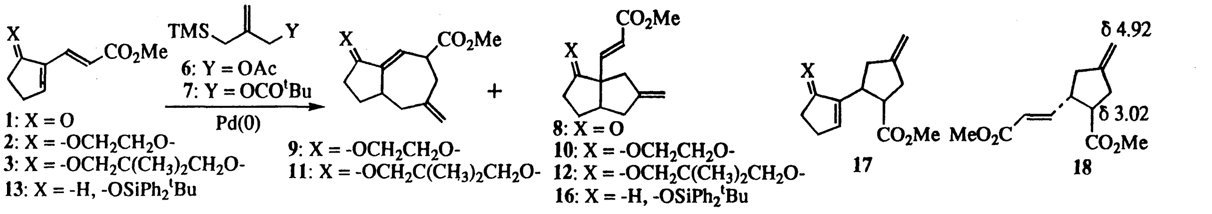


Table 1. Pd-Catalyzed Cycloaddition Reactions of **1**-**3** and **13** with TMM

Entry	Substrate	Conditions	Product
1	**1**	**6** (1 equiv), THF, 60 °C, 1.5 h	**8** (69%)
2	**2**	**6** (1 equiv), THF, 60 °C, overnight	recovered **2**, **9** (trace), **10** (trace)
3	**2**	**6** (2 equiv), toluene, 110 °C, 6 days	recovered **2** (19%), **9** (22%), **10** (34%)
4	**2**	**7** (4 equiv), THF, 60 °C, overnight	**9** (39%), **10** (48%)
5	**2**	Pd(0) (12.5 mol% dppp), **7** (6 equiv), THF, 60 °C, 24 h	**9** (37%), **10** (45%)
6	**3**	**7** (1 equiv), THF, 60 °C, 2 days, then **7** (0.4 equiv), 1 day, then **7** (0.3 equiv), 1 day, then **7** (0.2 equiv), 1 day	**11** (40%), **12** (28%)
7	**3**	**7** (2 equiv), THF, 60 °C, 6 h	**11** (48%), **12** (33%)
8	**3**	**7** (2 equiv), THF, 60 °C, overnight	**11** (26%), **12** (38%)
9	**13**	**7** (2 equiv), THF, 60 °C, 2 days, then **7** (2 equiv), 1 day	recovered **13**, a small amounts of products (not purified)
10	**13**	**7** (4 equiv), THF, 60 °C, 3 days	complex mixture, **16** (7%) was isolated.
11	**13**	**7** (6 equiv), THF, 60 °C, 4 days	decomposition

Derivatization of a 2-vinylcyclopentenone with bulky ketal substituents does serve to enhance seven-membered ring formation. The effect likely derives from a combination of both electronic and steric effects. Although the [4+3] *vs* [3+2] selectivity is not yet high enough, the total yield of the cycloaddition is good and seven-membered ring product yield is therefore modest. Also, ketals have the potential for asymmetric induction in this cycloaddition reaction by making them chiral. These studies suggest opportunities for further improvement of the [4+3] *vs* [3+2] cycloaddition by structural variation of the acceptor - especially the ketal unit - and perhaps by ligand variation in the donor TMM-PdL$_2$ complexes. However, for more efficient and successful design of the substrates, determination of the structure of the proposed zwitterion intermediate would be helpful. Extensions of this strategy are presently being evaluated.

We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility, University of California-San Francisco, supported by the NIH Division of Research Resources.

Reference

1) C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White,"The Total Synthesis of Natural Products," ed by J. W. Apsimon, Wiley, New York (1982), Vol 5; J. H. Rigby, "Studies in Natural Products Chemistry," ed by A. Rahman, Elsevier, New York (1988), Vol. 1, p. 545; S. P. Tanis, E. D. Robinson, M. C. McMills, and W. Watt, *J. Am. Chem. Soc.*, **114**, 8349 (1992); P. A. Wender, H. Y. Lee, R. S. Wilhelm, and P. D. Williams, *ibid.*, **111**, 8954 (1989); P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger, Jr., R. S. Wilhelm, and P. D. William, *ibid.*, **111**, 8957 (1989); P. Metz, S. Bertels, and R. Fröhlich, *ibid.*, **115**, 12595 (1993).

2) For some recent seven-membered ring syntheses, see: A. Rumbo, L. Castedo, A. Mouriño, and J. L. Mascareñas, *J. Org. Chem.*, **58**, 5585 (1993). G. A. Molander and K. O. Cameron, *ibid.*, **58**, 5931 (1993) and references cited therein.

3) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **12**, 819 (1973); H. M. R. Hoffmann, *ibid.*, **23**, 1 (1984); A. Hosomi and Y. Tominaga, "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon, New York (1991), Vol. 5, Chapt. 5.1; R. Noyori, *Acc. Chem. Res.*, **12**, 61 (1979).

4) B. M. Trost and D. T. MacPherson, *J. Am. Chem. Soc.*, **109**, 3483 (1987).

5) B. M. Trost, T. N. Nanninga, and D. M. T. Chan, *Organometallics*, **1**, 1543 (1982).

6) B. M. Trost and M. L. Miller, *J. Am. Chem. Soc.*, **110**, 3687 (1988); B. M. Trost and D. M. T. Chan, *ibid.*, **105**, 2326 (1983).

7) A. B. Smith, S. J. Branca, M. A. Guaciaro, P. M. Wovkulich, and A. Korn, *Org. Synth.*, Col Vol. 7, 271 (1990).

8) All new compounds have been fully characterized and have had elemental compositions determined by combustion analysis and/or high-resolution mass spectroscopy.

9) For reviews for Pd-catalyzed TMM cycloadditions, see: D. M. T. Chan, "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 5, Chapt. 3.2; P. Binger and H. M. Büch, *Top. Curr. Chem.*, **135**, 77 (1987); B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **25**, 1 (1986).

10) In a typical experiment, triisopropyl phosphite (10.4 µl, 0.042 mmol) was added to a suspension of palladium acetate (1.34 mg, 0.0060 mmol) in tetrahydrofuran (0.47 ml). To the resultant solution was added 1.5 M butyl lithium in hexane (8.01 µl, 0.0120 mmol). After 30 minutes, **3** (30.3 mg, 0.120 mmol) was added followed by 7 (54.8 mg, 0.240 mmol). The mixture was heated to 60 °C for 6 h. The reaction mixture was cooled and concentrated *in vacuo*. Column chromatography (SiO$_2$ - 10% ether/hexane) gave 12.1 mg (33%) of **12** (Rf = 0.7 (SiO$_2$-tlc; 50% ether-hexane)) and 17.8 mg (48%) of **11** (Rf = 0.6 (SiO$_2$-tlc; 50% ether-hexane)).

11) **11**: colorless oil; IR (neat) 2944, 2856, 1730, 1640, and 1435 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.757 (s, 3H), 1.28 (s, 3H), 1.33-1.42 (m, 1H), 1.66-1.74 (m, 1H), 1.91-2.00 (m, 2H), 2.24 (t, J = 12 Hz, 1H), 2.31-2.41 (m, 2H), 2.47-2.56 (m, 1H), 2.68 (d, J = 12 Hz, 1H), 3.15 (dddd, J = 8.8, 4.3, 2.2, 2.2 Hz, 1H), 3.46-3.52 (m, 2H), 3.61-3.68 (m, 2H), 3.72 (s, 3H),, 4.79 (bs, 1H), 4.82 (bs, 1H), and 6.45 (dd, J = 3.6, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) 22.07, 22.92, 29.30, 29.45, 30.19, 39.25, 41.74, 42.83, 46.25, 51.95, 72.07, 72.60, 106.0, 112.4, 124.8, 148.8, 150.5, and 174.6.

12) **12**: colorless oil; IR (neat) 2944, 2860, 1720, 1645, and 1434 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.72 (s, 3H), 1.16 (s, 3H), 1.29-1.37 (m, 1H), 1.70 (ddd, J = 13.3, 9.6, 9.6 Hz, 1H), 1.97 (dddd, J = 13.2, 9.3, 9.3, 9.3 Hz, 1H), 2.15 (d, J = 14.8 Hz, 1H), 2.31-2.42 (m, 2H), 2.48-2.59 (m, 2H), 2.65 (dd, J = 17.4 Hz, 1.8 Hz, 1H), 3.38-3.43 (m, 2H), 3.50 (d, J = 11.2 Hz, 1H), 3.60 (d, J = 11.6 Hz, 1H), 3.73 (s, 3H), 4.84 (bs, 2H), 5.79 (d, J = 16 Hz, 1H), and 7.46 (d, J = 16 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) 21.99, 22.83, 26.84, 28.41, 30.04, 39.98, 40.38, 44.20, 51.32, 62.14, 70.91, 72.93, 106.7, 110.2, 118.7, 150.7, 152.3, and 167.4.

(Received August 19, 1994)