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SYNTHESIS OF 4-METHYLENE-1-CYCLOPENTENES

Barry M. Trost*, James M. Balkovec and Steven R. Angle

McElvain Laboratories of Organic Chemistry, Department of Chemistry
University of Wisconsin, 1101 University Avenue, Madison, WI 53706

SUMMARY: 4-Methylene-1-cyclopentenes are available via the cycloaddition of palladium-trimethylenemethane to substituted bicyclo[2.2.1]hepta-2,5-dienes followed by flash vacuum thermolysis.

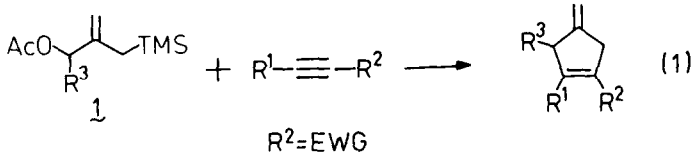
The isolation of a multitude of cyclopentanoid natural products has spurred on the development of new methods for the synthesis of highly functionalized cyclopentanes. A recent report by Binger[1] describing the synthesis of 4-methylene-1-cyclopentenes by the Ni(0)-catalyzed codimerization of methylenecyclopropanes and disubstituted acetylenes prompts us to disclose the results of our study in this area.

As a rapid entry into the methylenecyclopentenes, a Pd(0) mediated trimethylenemethane[2] (Pd-TMM) addition to an acetylene was envisioned (eq. 1). The regioselective cycloaddition of this complex to olefins possessing an electron withdrawing group is well precedented[3]. A related reaction with acetylenic acceptors should proceed to give a cycloadduct as depicted in eq. 1. However, all attempts to effect cycloaddtion as in eq. 1 led to unidentified products. The success of the Pd-TMM addition to olefinic acceptors led to temporarily masking the acetylene as an olefin by forming its Diels-Alder adduct with cyclopentadiene, carrying out the cycloaddition, and then regenerating the desired unsaturation by a retro-Diels-Alder reaction[4] to create the equivalent transformation as in Scheme 1. Obtention of a mixture of products 3 derived from exo and endo attack on 2 (albeit favoring exo attack) is of no consequence since the final product 4 converts these Sp^3 centers into a cyclopentene double bond.

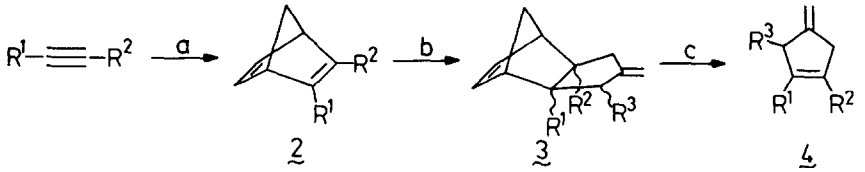
As Table 1 shows, cycloaddition to the readily available norbornadienes proceeds well in most cases using our standard in situ method for generating the catalyst by mixing palladium acetate with triisopropyl phosphite in which the latter serves as both reducing agent of Pd(+2) and ligand for Pd(0). As entry 4

shows, if the normal ratio of 1:2 is increased from 1:1 to 1.2:1 then the yield of 95% at 91% conversion transforms to the same yield at complete conversion.

Flash vacuum thermolysis (FVT) completes the sequence as summarized in Table 2. Indeed, the thermolysis can be simply a distillation of the adduct 3 during work-up to yield the desired 3-methylenecyclopentenes in which the product 4 is



Scheme 1. 4-Methylene-1-Cyclopentene Synthesis



a) C_5H_6 b) $Pd(OAc)_2$, $(i\text{-}PrO)_3P$, 1, THF, reflux c) FVT 530-755°

Table 1. Pd-TMM Addition to Norbornadienes 2[a]

Entry	Compound 3	R^1	R^2	R^3	exo:endo[b]	Yield%	Yield Based (On Recovered Starting Material)
1	a	CO_2CH_3	CO_2CH_3	H	3-4:1	84	(96)
2	b	CO_2CH_3	CO_2CH_3	CH_3	5:1	71	(95)
3	c	H	CO_2CH_3	H	4-5:1	85	(96)
4	d	H	$CO_2C_2H_5$	H	4.6:1	87	(95),95[d]
5	e	H	COPh	H	----[c]	29	(46)
6	f	H	SO_2Ph	H	----[c]	7	(27)
7	g	$-CH_2OCO-$		H	----	0	

a) Reactions carried in refluxing THF using 1-7 mol % of palladium acetate and, 7-8 eq. of triisopropylphosphite relative to palladium. Ratio of 1:2 is 1 unless otherwise noted. b) Determined by ^1H nmr spectroscopy. c) Ratios could not be determined. d) Utilized 1.2 eq. of 1.

Table 2. Flash Vacuum Thermolysis of Cycloadducts

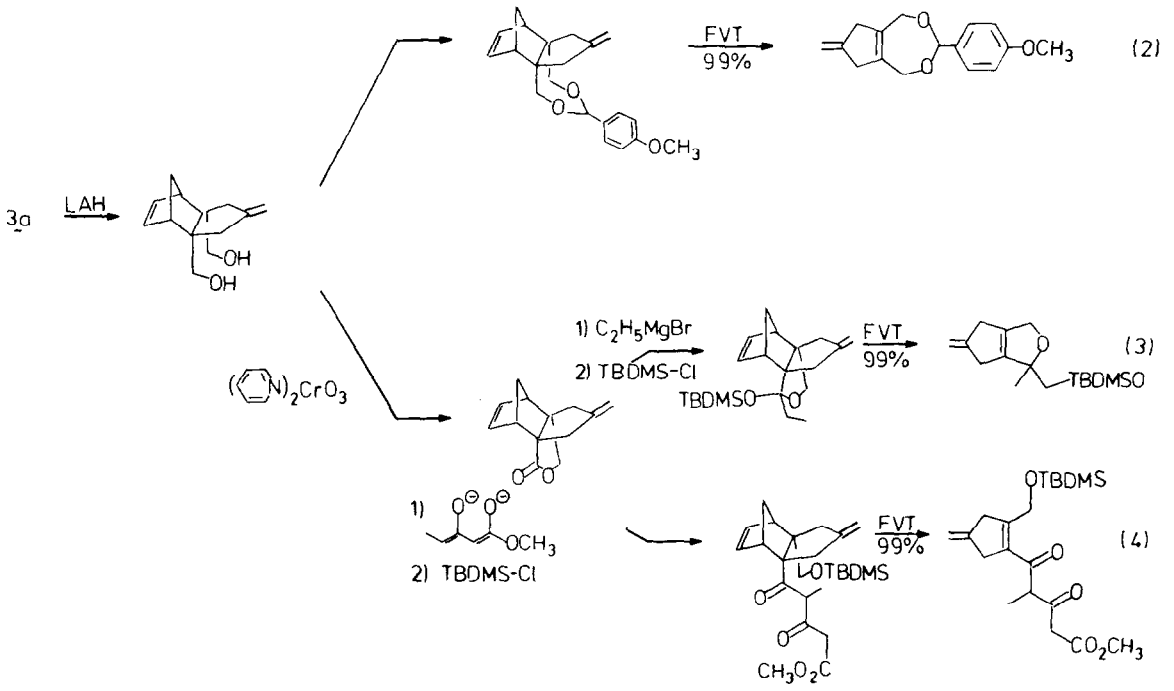
Entry	Cycloadduct 3	T(°C)/P(torr)	Product 4	Yield	Overall (from acetylenes)
1	a	550/2	a	100	(92)
2	b	530/0.1	b	94	(86)
3	c	600/2	c	89	(50)
4	d (R=C_2H_5)	755/0.02	d (R=H)[a]	58	(27)
5	e	560/0.03	e	62	(26)
6	f	560/0.03	f	72	(13)
7	g[b,c]	580/0.03	g[b]	95	(84)
8	h[d,e]	575/0.03	h[d]	100	(92)

a) Elimination of ethylene accompanied retro-Diels-Alder reaction.
b) R^1, R^2=$CH_2OC(=O)$. c) 3g prepared by Collins oxidation of 3h.
d) R^1=R^2=CH_2OH. e) 3h prepared by LAH reduction of 3a.

obtained virtually pure directly. The regioselective production of 4b is quite noteworthy and contrasts with the low regioselectivity of the co-oligomerization reaction of methylenecyclopropane. The high yield preparation of 4c also contrasts with the co-oligomerization which fails with methyl propiolate.

The utility of this approach also stems from the ease of manipulation of the intermediate adducts prior to unmasking. Whereas, the lactone 3g was not available by the direct cycloaddition to the butenolide 2g, it is easily available from the diester 3a by simple reduction-oxidation (see footnotes, Table 2). Further utility of the intermediate adducts for synthesis is revealed in eq. 2,3, and 4. In each case, the FVT (590°, 0.005 min) proceeded virtually quantitatively. Combined with the ready availability of the initial adduct on multigram scales in 95-6% isolated yields clearly makes such an approach highly practical.

This regiocontrolled synthesis of the 3-methylene cyclopentenes facilitates the exploration of the synthetic utility of this fascinating and versatile building block.



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