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STERIC IMPEDENCE IN THE 1,3-PHOTOCYCLOADDITION REACTION BETWEEN CYCLOPENTENE AND ANISOLE DERIVATIVES

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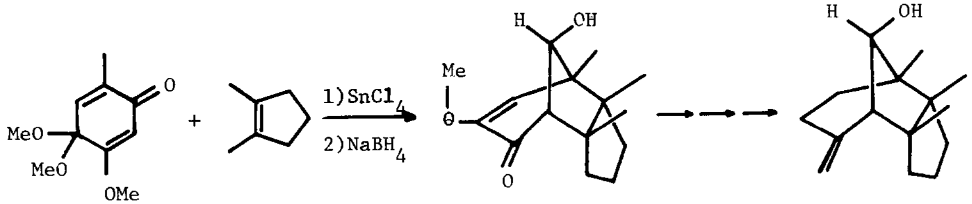
Summary: *The detrimental effect of increasing substitution on the olefin and aromatic partners for the title reaction is demonstrated; several transformations of the resulting photoadducts are described.*

Recent interest in the synthesis of the sesquiterpene gymnomitrol (**1**)[1] [in particular the carbon-carbon skeletal bond construction demonstrated in the Büchi synthesis (eq 1)][1b] and in synthetic applications of the 1,3-photocycloaddition reaction of olefins with benzene derivatives[2] [as exemplified by the addition of cyclopentene (**3**) to anisole (**2**) to give ketone **5** after hydrolysis of the 1,3-adduct **4** (see Scheme)][3] prompt this report of efforts in these areas.

(eq 1)



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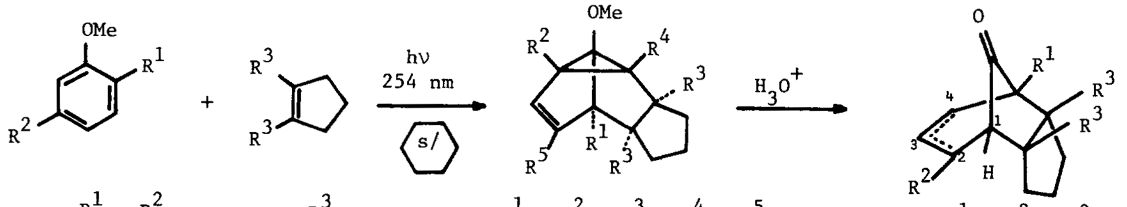
o-Methylanisole (**6**) was 1,3-photoadded (254 nm, cyclohexane) to cyclopentene (**3**) to give a mixture of major and minor adducts **7** (δ 5.56, 1H, br d, J=6 Hz; 5.39, 1H, br d, J=6 Hz; 3.42, 3H, s; 2.92, 2H, br m; 2.07, 2H, br s; 1.3-1.8, 6H, m; 1.25, 3H, s) and **8** (δ 5.65, 2H, m; 3.38, 3H, s; 2.5-3.2, 3H, m; 1.70, 1H, br s; 1.3-1.8, 6H, m; 1.25, 3H, s) (∿2:1) in spite of the report that **6** does not enter into this reaction.[3] However, the rate of this addition was somewhat slower and the yield lower than the corresponding reaction of anisole itself. Specifically after hydrolysis the mixture of ketone olefins **9** (2:1 ratio; homogeneous by tlc, gc; δ 5.55, 2H, br s (major); 5.55, 1H, m (minor); 5.25, 1H, br d, J=9 Hz (minor); 1.07, 3H, s (major); 1.05, 3H, s (minor)) was obtained in 11% distilled yield when irradiation was continued for 7 days. In contrast, the unsubstituted ketone **5** was isolated in 16% yield from anisole (cf 68% for the two steps in ref 3) after 3 days of irradiation. Reduction of ketones **9** (eq 2, NaBH$_4$, 0°C) provided a 2:1 mixture of alcohols **10** and **11**. That these were regioisomeric olefins and not C$_{11}$ epimeric alcohols was suggested by the similarity of the H$_{11}$ methine resonance in the pmr of each (δ 3.72, $W_{\frac{1}{2}h}$=10 Hz for **10** and δ 3.60, $W_{\frac{1}{2}h}$=11 Hz for **11**) and the upfield shift of H$_8$ in **11** relative to **10** (δ 5.65, 2H, m for H$_8$, H$_9$ in **10** and δ 5.16, ddd, $J_{8,9}$=10, $J_{8,10\beta}$=3, $J_{8,10\alpha}$=1.5 Hz for H$_8$ and δ 5.77, dd, $J_{9,8}$=10, $J_{9,10\alpha}$=3 Hz for H$_9$ in **11**). This assignment was confirmed by catalytic reduction of a mixture of **10** and **11** as well as of their derived acetates **12** and **13** to the single alcohol and acetate **14** and **15**, respectively. Moreover, the mixture of **10** and **11** could be partially isomerized into the two new alcohols **16** and **17** upon exposure to Al(iPrO)$_3$ in iPrOH/CH$_3$COCH$_3$ at 85°C. The proton at C$_{11}$ in each of the latter was now a narrower multiplet (δ 4.98, $W_{\frac{1}{2}h}$=3 Hz and δ 5.03, $W_{\frac{1}{2}h}$=3 Hz) since long rangecouplings to H$_8$ and H$_{10\alpha}$ were now re-

Scheme



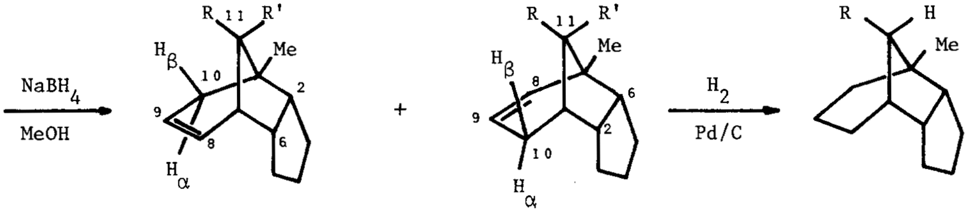
	R^1	R^2
2	H	H
6	Me	H
23	Me	Me
26	H	CH$_2$OMe

	R^3
3	H
20	Me

	R^1	R^2	R^3	R^4	R^5
4	H	H	H	H	H
7	Me	H	H	H	H
8	H	H	H	Me	H
24	Me	Me	H	H	H
27	H	CH$_2$OMe	H	H	H
28	H	H	H	H	CH$_2$OMe

	R^1	R^2	R^3
5	H	H	H
9	Me	H	H
21	Me	H	Me
22	H	H	Me
25	Me	Me	H $\Delta^{2,3}$

(eq 2) **9**



	R	R'
10	OH	H
12	OAc	H
16	H	OH

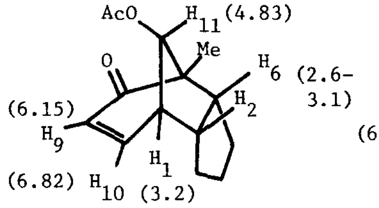
	R	R'
11	OH	H
13	OAc	H
17	H	OH

	R
14	OH
15	OAc

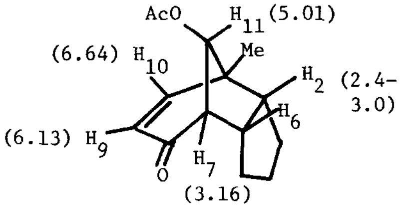
moved. This observation added strength to the assignment of stereochemistry at the carbinol carbon as well as at C_2 and C_6 (endo cyclopentane ring).

A transformation which boded well for a potential application of this chemistry to a gymnomitrol (**1**) synthesis was the regioselective allylic oxidation of the mixture of acetates **12** and **13** with excess $CrO_3 \cdot py$ complex (CH_2Cl_2, RT, 3 days)^4 which gave a minor, less polar enone **18** (7%) and its regioisomer **19** (61%). The product ratio can be correlated with the anticipated relative ease of attack by the oxidizing species on the electron deficient allylic radical or cation. That approach must be perturbed away from perpendicular by the syn acetoxyl substituent to the extent that hindrance by the allylic methyl group favors attack at the remote allyl terminus thus leading preferentially to **19**.

$J_{1,2}$ = 8 Hz
$J_{1,10}$ = 6 Hz
$J_{1,11}$ = 4.5 Hz
$J_{9,10}$ = 10 Hz
$J_{10,11}$ = 2.5 Hz



18



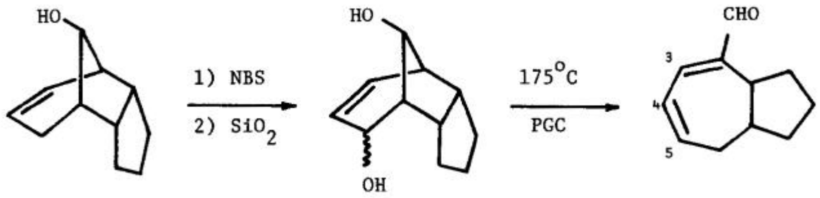
19

$J_{6,7}$ = 7 Hz
$J_{7,9}$ = 2 Hz
$J_{7,11}$ = 5 Hz
$J_{9,10}$ = 10 Hz
$J_{10,11}$ = 2.5 Hz

This regioselective oxidation suggested that facile access to the gymnomitrol (**1**) skeleton would be in hand if 1,2-dimethylcyclopentene (**20**) could be induced to photoadd to *o*-methylanisole (**6**) to give the trimethylated ketone **21** (see Scheme). Initially the tetrasubstituted olefin **20** was reacted with anisole (**2**) itself. After hydrolysis and repeated gas chromatographic purification, an abysmal 0.1% yield (0.7 mg) of a mixture ($\sim$1:5) of ketones assigned structures **22** and **22**' (exo isomer of **22**) was obtained (δ 5.60, 2H, m; 2.70, 2H, m; 1.14, 1.13, s's for CH_3's of minor isomer; 0.97, 0.95 s's for CH_3's of major isomer). In view of the greatly diminished reactivity and yield in the addition of 1,2-dimethylcyclopentene (**20**) to anisole, it was not surprising to learn that 1,3-photoadducts of **20** with *o*-methylanisole could not be isolated either before or after acid hydrolysis. Higher molecular weight hydrocarbons were the only observed products (cf. ref 3).

Finally, in the course of this work several other 1,3-photoadditions and transformations of the resulting adducts were observed. These include: the addition of 2,5-dimethylanisole (**23**) to cyclopentene to give a single cyclopropane **24** (δ 5.40, 2H, AB, J_{AB}=6 Hz; 3.46, 3H, s; 2.87, 2H, m; 1.75, 1H, m; 1.3-1.7, 6H, m; 1.27, 3H, s; 1.22, 3H, s) and its hydrolysis to ketone **25** (see Scheme; 2% yield after Kugelrohr distillation; δ 5.20, 1H, m; 1.3-2.6, 11H, m; 1.65, 3H, ddd, J= 2,2,2Hz; 1.04, 3H, s); the addition of *m*-methoxymethylanisole **26** to cyclopentene to give adducts **27** (δ 5.74, 2H, m; 3.48, 2H AB, J_{AB}=13 Hz; 3.37, 3H, s; 3.34, 3H, s; 3.18, 3H, m; 1.95, 1H, d, J=7 Hz; 1.6-2.3, 6H, m) and **28** (δ 5.63, 1H, m; 3.95, 2H, br s; 3.35, 3H, s; 3.28, 3H, s; 2.8-3.3, 3H, m; 2.19, 1H, dd, J-8, 6 Hz; 1.98, 1H, dd, J=8, 3 Hz; 1.7-2.3, 6H, m) in a 2:1 ratio (see Scheme); and the allylic oxidation of alcohol **29** (from **5** + $NaBH_4$) with NBS which provided diol **30** upon silica gel chromatography (eq 3, 47%). This diol fragmented cleanly to dienal **31** (δ 9.34, 1H, s; 6.63, br d, J=7 Hz, H_3; 6.30, 1H, m, H_5; 6.08, dd, J=11, 7 Hz, H_4; 3.0, 1H, m; 2.2, 3H, m;

(eq 3)



29 30 31

1.3-2.0, 6H, m) when subjected to prepatative gas chromatography at 175°C.

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