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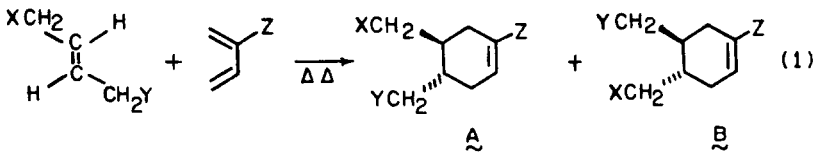
# A VINYL SULFONE-MEDIATED DIELS-ALDER APPROACH TO THE FULLY REGIOCONTROLLED ELABORATION OF 4,5-DISUBSTITUTED 2- AND 3-CYCLOHEXENONES

Leo A. Paquette* and William A Kinney

*Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210*

*Summary* Reported here is a scheme which enables one to prepare independently 4,5-disubstituted 2- or 3-cyclohexenones where the nature of the pendant sidechains can be widely varied

Restrictions persist on the role of unactivated carbon-carbon double bonds as useful centers of reactivity in Diels-Alder reactions because of the lack of π-donor-acceptor complementarity The problem can be exacerbated by a total lack of stereoselectivity in those few examples where forcing conditions have been successfully applied (eq 1) In an effort to lift this synthetic

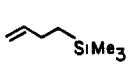
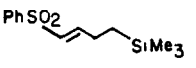
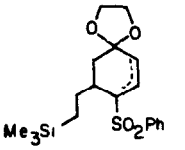
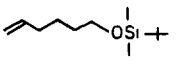
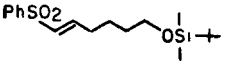
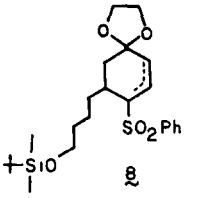
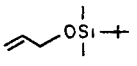
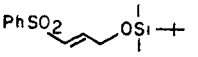
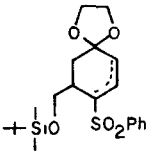



A B (1)

constraint, we have developed a relatively short, indirect solution which has its foundations in the knowledge that (a) phenyl vinyl sulfone can serve as a convenient ethylene and terminal olefin equivalent in [4+2] cycloadditions[1]; (b) α,β-unsaturated sulfones are captured by unsymmetrical dienes with high regioselectivity[1,2], and (c) γ-sulfonylcyclohexenone ketals undergo regioselective γ-alkylation[3] Through combination of these cumulative experiences, great simplification is achieved in gaining access to pure adducts of either the A or B type The breadth of the methodology to be described should serve well as a useful vehicle for total synthesis.

Our general strategy begins with the efficient photochemical selenosulfonation[4,5] of a functionalized terminal alkene, Diels-Alder cycloaddition of 1-3 with Danishefsky's diene,[6] and direct ketalization of these adducts to give 7-9 (Table I, yields not optimized).[7] Due to the acid lability of the tert-butyldimethylsilyloxy substituent in two of these substrates, the use of p-toluenesulfonic acid as ketalization catalyst necessitated resilylation prior to

Table I Olefin Activation and Conversion to 4-Phenylsulfonylcyclohexenone Ketals.

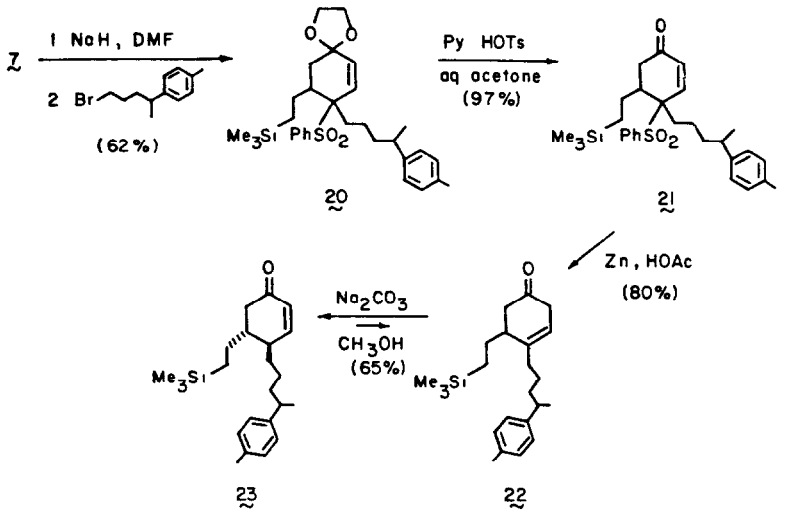
| Olefin | Selenosulfonation product | Yield, % | Ketal | Yield, % |
|---|---|---|---|---|
|  |  | 93 |  | 88 |
| 1 | 4 | | 7 | |
|  |  | 89 |  | 35 |
| 2 | 5 | | 8 | |
|  |  | 85 |  | 74 |
| 3 | 6 | | 9 | |

product isolation Under these conditions, the β,γ-unsaturated ketals are formed as the predominant products Since the subsequent step involves deprotonation (NaH, DMF) and alkylation, the isomeric ketals are directly usable without purification.

Following arrival at 7, its anion was prepared and alkylated as shown in Scheme I Notwithstanding the more congested steric environment at the α site in this allylic intermediate, the charge affinity of the sulfonyl group dominates to deliver 20 rather cleanly. Deketalization is followed by reductive desulfonylation with zinc in acetic acid[9] Under these conditions, the β,γ enone 22 is formed efficiently, requiring independent equilibration to arrive at 23

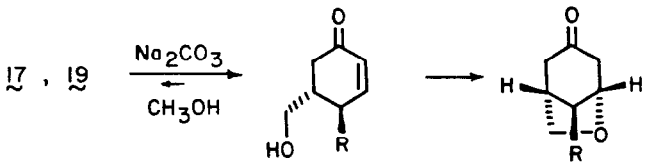
For the remaining syntheses summarized in Table II, the phenylsulfonyl group was cleaved (6% sodium amalgam in $Na_2HPO_4$-buffered methanol[10]) prior to hydrolysis of the ketal This sequencing was followed to deter possible unwanted double bond migration from allylic $C_4$ substituents to an intra-ring position during conversions of the 21 → 22 type, e g , with 11

SCHEME I




The somewhat reduced alkylation yields achieved during use of more bulky agents such as the 3-(trimethylsilyl)-2-butenyl and geranyl bromides (Table II) are attributed to reasonably competitive α-alkylation due to steric interaction with $R^1$ Some dialkylated product therefore is formed The data given refer to the amounts of pure γ-alkylated product obtained subsequent to MPLC purification.

In those equilibration studies involving the β,γ-cyclohexenones 17 and 19 which carry a methylol sidechain at $C_5$, intramolecular cyclization to the oxabicyclo[3 2 1]octanones 25 occurs

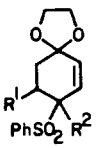
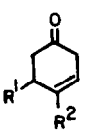
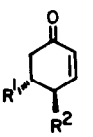
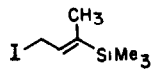
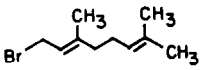
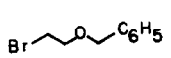



a, R=geranyl ; b, $R=(CH_2)_2OCH_2C_6H_5$

partially during base treatment[11] This phenomenon is expectedly not witnessed when the hydroxyl group is held more remotely as in 14 The chromatographic separation of 24 from 25 can be readily accomplished

Although a pair of 4,5-disubstituted 2-cyclohexenones having $R_1$ and $R_2$ reversed has not been prepared in this study, the potential for functionalizing either position at will is

Table II. Sequential Alkylation, Reduction, Hydrolysis, and Equilibration of 7-9.

| Ketal | Electrophile |  | Yield, % |  | Yield, % |  | Yield, % |
|---|---|---|---|---|---|---|---|
| 7 |  | 10, $R^1$=$CH_2CH_2SiMe_3$, $R^2$=$CH_2CH$=$CH_2$ | 71 | 11, $R^1$=$CH_2CH_2SiMe_3$, $R^2$=$CH_2CH$=$CH_2$ | 72 | 12, $R^1$=$CH_2CH_2SiMe_3$, $R^2$=$CH_2CH$=$CH_2$ | 51 |
| 8 |  | 13, $R^1$=$(CH_2)_4OSiMe_3$, $R^2$=$CH_2CH$=$C(CH_3)Si$+ | 35 | 14, $R^1$=$(CH_2)_4OH$, $R^2$=$CH_2CH$=$C(CH_3)SiMe_3$ | 69 | 15, $R^1$=$(CH_2)_4OH$, $R^2$=$CH_2CH$=$C(CH_3)SiMe_3$ | 67 |
| 9 |  | 16, $R^1$=$CH_2OSi$+, $R^2$=geranyl | 41 | 17, $R^1$=$CH_2OH$, $R^2$=geranyl | 71 | see text | |
| 9 |  | 18, $R^1$=$CH_2OSi$+, $R^2$=$(CH_2)_2OCH_2C_6H_5$ | 29 | 19, $R^1$=$CH_2OH$, $R^2$=$(CH_2)_2OCH_2C_6H_5$ | 75 | see text | |

clearly present In future research, we plan to develop this methodology for use in macrolide synthesis, curvularin serving as one of the initial targets[12]

## References and Notes


(1) Carr, R V. C., Paquette, L. A *J Am Chem. Soc.* 1980, *102*, 853.

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(5) In our hands, the photochemical procedure gave superior yields to the thermal alternative Back, T. G., Collins, S. *Tetrahedron Lett.* 1980, 2215, *J. Org. Chem.* 1981, *46*, 3249

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(7) The structures of all new compounds are in accord with (a) their infrared, $^1H$ NMR, and $^{13}C$ NMR spectra and (b) combustion analysis and/or accurate mass spectral molecular weight measurements.

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(11) With 17 45% of 24a and 12% of 25a. With 10. 35% of 24b and 24% of 25b.

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