

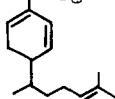
A NEW SYNTHON FOR THE REGIOSPECIFIC γ -ALKYLATION OF
 2-CYCLOHEXENONES. APPLICATION TO THE SYNTHESIS OF ZINGIBERENOL
 AND OXYGENATED BICYCLO[3.5.1]NONANES

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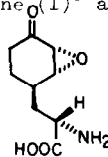
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Summary: The regiospecific γ -alkylation of γ -sulfonylcyclohexenone ketals is described and applied to various synthetic objectives.

The utilitarian dienophilic properties of phenyl vinyl sulfoxide¹ and sulfone² in Diels-Alder reactions have recently been demonstrated in this laboratory. As part of this synthetic program, we have sought to devise a versatile and expedient protocol which would result in net γ -alkylation of 2-cyclohexenones. At present, this important class of intermediates is necessarily generated indirectly.³⁻⁸ Although certain of these alternative procedures are highly imaginative, none appears entirely general. Consequently, synthetic schemes involving 4-substituted 2-cyclohexenones, e.g., those targeted toward zingiberene⁽¹⁾⁹ and anticapsin⁽²⁾,¹⁰ are somewhat



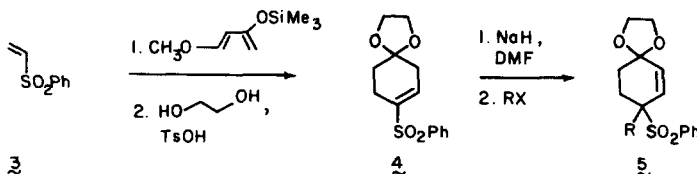
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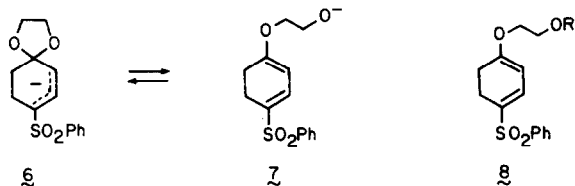
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protracted. It is well documented that complications arise in attempts at direct alkylation of 2-cyclohexenones because their kinetic dienolates react at the α' position.¹¹ Thermodynamic dienolates suffer from a propensity to undergo irreversible C-alkylation at the α position, even when this site is already substituted.¹² The presence of an activating carboxylate group at C-4 as in Hagemann's ester does not obviate the difficulty of achieving intermolecular γ -alkylation.¹³ β -Enamino ketones derived from secondary amines constitute the only exception.^{14,15}

Our solution to this long-standing problem, which was inspired by Julia's and Lansbury's pioneering application of sulfonyl substituents to the regiochemical control of alkylation, is embodied in ketal sulfone **4** (mp 77-78°C). This synthon is readily accessible in 85% overall yield by [4 + 2] cycloaddition of **3** to Danishefsky's diene¹⁶ (C₆H₆, reflux, 28h) and direct ketalization of the adduct (C₆H₆, reflux, 23h).¹⁷ The alkylations of **4** (NaH, DMF) proved to be especially clean in all of the examples listed in Table I (yields unoptimized). In the case of ethyl 5-iodopentanoate where additional acidic protons are present, inverse addition was utilized for yield maximization. Although the heightened nucleophilicity of the α -sulfonyl

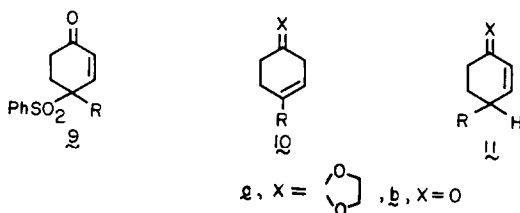


carbanion center in 6 has ample precedent,¹⁸ the observed regioselectivity may be additionally fostered by steric congestion adjacent to the spiro center. Analogous methylation of 9 (R=H), available by direct acid hydrolysis of the Diels-Alder adduct, gave a 56:44 mixture of α -alkylated and α,γ -dialkylated 4-phenylsulfonyl-2-cyclohexenones.¹⁹ It is especially relevant



that 6 shows little tendency to react via its ring-opened form 7 to give products of type 8 when primary halides or sulfonate esters are involved.

Deketalization of 5 with pyridinium *p*-toluenesulfonate (PPTS) in hot acetone²⁰ led efficiently to 9. However, the application of various desulfonylation methods to 9 did not proceed as well as desired. This complication was obviated by effecting the reductive desulfonylation of ketal sulfones 5 with 6% sodium amalgam in Na₂HPO₄-buffered methanol.²¹ These reactions were usually complete within 30 min at room temperature, the pendant functional groups were not chemically altered, and yields of the pure products generally bordered on quantitative. A preponderance of the more thermodynamically favored β,γ -unsaturated ketals 10a was routinely observed







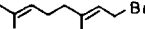


(¹H NMR analysis, Table I). Acid hydrolysis of these mixtures (1 mmol ketal and 50 mg TsOH in 12 ml of 95% ethanol; reflux 15-20h) delivered the target cyclohexenones 10b and 11b. The equilibrium distribution of structurally simpler derivatives has been examined by others.²²

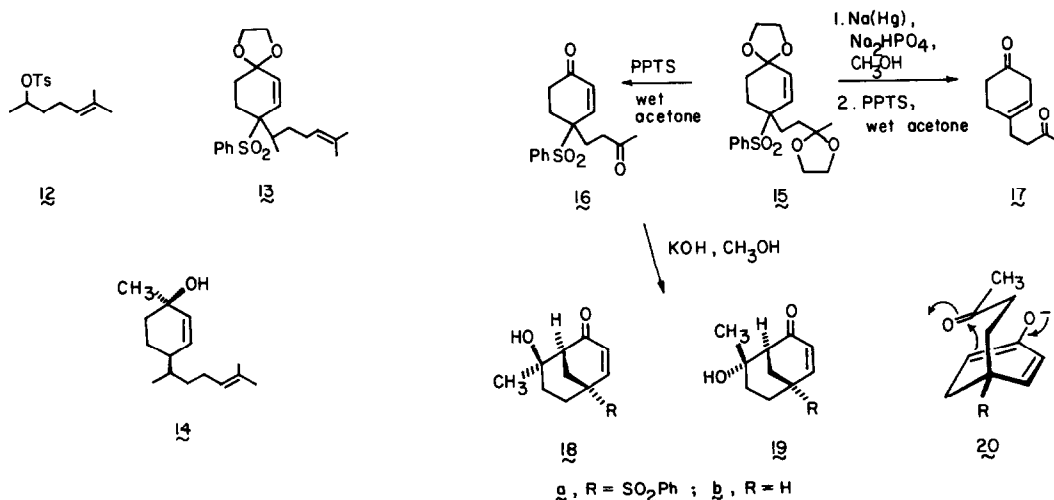
With the preceding methodology as a guide, zingiberenol (14), a sesquiterpene alcohol recently isolated from the essential oil of *Zingiber officinale* Rosc,²³ was conveniently synthesized. Alkylation of 4 with secondary tosylate 12²⁴ as before gave 13 (47%) as a mixture of diastereomers.²⁵ Accompanying 13 was the O-alkylated derivative 8 [R = 2-(6-methyl-5-heptenyl), 15%] which is now encountered because of the obvious steric disadvantages of coupling a tertiary nucleophilic carbon to a secondary electrophilic center. Following desulfonylation and hydrolysis (PPTS, wet acetone;²⁶ NaOCH₃, CH₃OH) to the conjugated enone, reaction with methyl lithium furnished 14 and the *cis* isomer (2.4:1), separable by medium pressure liquid chromatography.²⁷

In a second application of the γ -alkylation sequence, 4 was condensed with 4-bromo-2-butanone ethylene ketal²⁸ and the resultant 15 (83%) was partitioned between 16 (90%) and 17 (79% overall). Upon exposure of 16 to alcoholic potassium hydroxide, access to the bicyclic keto alcohols 18a (mp 166-168°C, 72%) and 19a (mp 178-179°C, 11%) was realized. Structural assignment to the individual epimers was initially based on the premise that aldol condensation would occur

Table I. Regiospecific γ -Alkylation of 2-Cyclohexenones.

Electrophile	alkylation yield, % of $\underline{2}$	-----desulfonylation----- yield, %	ratio $\underline{10a}:\underline{11a}$	-----hydrolysis----- yield, %	$\alpha\beta$: $\beta\gamma$ ratio
CH_3I	83	89	59:41	74	80:20
	77	98	69:31	73	61:39 ^a
	91	100	66:34	87	62:38
	81	100	68:32	83	68:32
	89	90	63:37	82	70:30
	92	92	67:33	87	47:53
	76	95	64:36	72	69:31
	94	100	62:38	93	36:64 ^b
$\text{EtOOC(CH}_2)_4\text{I}$	92	71	56:44	76	69:31

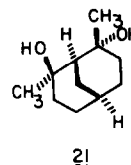
^aValues derived from product quantities isolated because accurate ^1H NMR integration was not possible. ^b Longer heating gave rise to an equilibrium ratio of 69:31.



preferentially from that conformation having opposed dipoles as in $\underline{20}^{\text{29}}$. This conclusion was supported by the more highly shielded nature of the methyl singlet in $\underline{18a}$ (δ 1.20; compare δ 1.39 for $\underline{19a}$) and later established by: (a) analogous conversion of $\underline{17}$ to $\underline{18b}$ (mp 92-93.5°C, 51% δ_{CH_3} 1.21); (b) catalytic hydrogenation of $\underline{18b}$; and (c) reaction of the dihydro product with methyl-lithium to give $\underline{21}$ which was devoid of a molecular plane of symmetry (^{13}C NMR analysis).

Since the second methyl group in 21 is certain to have entered from the exo direction, the original alkyl substituent is required to be endo.

The methodology outlined herein provides the groundwork for numerous additional synthetic applications, some of which we hope to report on in the near future.³⁰



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- (25) Separation into the two pure components by medium pressure liquid chromatography can be accomplished readily.
- (26) Pure β,γ -unsaturated cyclohexenone was obtained under these conditions.
- (27) Although our sample of 14 consisted of a mixture of diastereomers, the IR spectrum was superimposable upon the published one.²³
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- (29) This conclusion was based on the assumption that steric factors within 20 would dominate over the ability of potassium ion (in ethanol solution) to cooperatively ligate both the enolate and carbonyl moieties. Aldol stereoselection is known to be effectively controlled in the latter fashion, particularly if lithium is the counterion (not examined in the present study).
- (30) This work was assisted financially by a grant from the National Cancer Institute to which we are grateful.