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Probing the Formation of Bicyclo[4.2.0]octan-1-ols

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Reaction of lithium enolates of simple ketones with (±)-phenyl vinyl sulfoxide has potential for the convergent construction of complex fused ring systems containing a bicyclo[*n*.2.0]alkan-1-ol. The formation of sulfinylbicyclo[4.2.0]octan-1-ols **1**−**3** from the lithium enolate of cyclohexanone with (±)-phenyl vinyl sulfoxide or (*R*)-(+)-*p*-tolyl vinyl sulfoxide **18** was used to probe the mode of this novel cyclization reaction. Using phenyl vinyl sulfoxide, variations in the reaction lighting and solvent were investigated, in conjunction with radical trapping (TEMPO) and isotope labeling (deuterium) experiments. Cyclization to form sulfinylbicyclooctanols **1**−**3** is likely to proceed via an intermediate that ring closes to the bicycloalkanol anion **11** and was presently favored by the use of solvents such as THF or DME.

Introduction

Bicyclo[*n*.2.0]alkan-1-ols are an integral part of the framework of various natural product compounds and are synthetic precursors to other natural products. Examplary of the incorporation into natural products are functionalized bicyclo[3.2.0]heptan-1-ols contained within spatane-type diterpenes[1,2] and bourbonene-derived compounds;[3] functionalized bicyclo[4.2.0]octan-1-ols contained within terpenes,[4] diterpenes,[5] sesquiterpenes,[6] sesquiterpenoids,[7] diterpenoids,[8] indole-isoprenoids,[9] and neolignans;[10] functionalized bicyclo[5.2.0]nonan-1-ols contained within sesquiterpenoids;[11] and functionalized bicyclo[6.2.0]decan-1-ols contained within neolignans[10] and sesquiterpenes.[7d,12] Given the synthetic challenge of such natural product structures, the development of new synthetic methodology toward viable synthetic precursors of natural products is of constant interest.

Recently we have shown that, using accurate control of temperature, concentration, and reaction time, the reaction of the enolate generated from cyclohexanone and LDA at −78 °C in THF, in the dark, with (±)-phenyl vinyl sulfoxide gave novel sulfinylbicyclo[4.2.0]octan-1-ols **1**−**3** and monoalkylated cyclohexanone **4** in a 95:5 ratio (Scheme 1).[13] The relative stereochemistries of the sulfinylbicyclooctanols **1**−**3** were established by X-ray structural determination.[13]

In a further study we demonstrated that a range of simple ketones of varying ring sizes (five- to eight-membered) can react likewise with phenyl vinyl sulfoxide. Upon oxidation with *m*-chloroperoxybenzoic acid (MCPBA), sulfonylbicyclo[3.2.0]heptan-1-ols **5** and **6**, sulfonylbicyclo[5.2.0]nonan-1-ols **7** and **8**, and sulfonylbicyclo[6.2.0]decan-1-ols **9** and **10** were obtained in partially optimized yields of 27.5−70% (Chart 1).[14] In addi-

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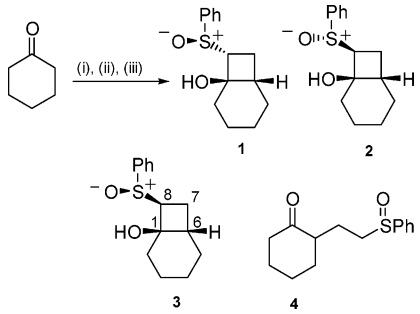
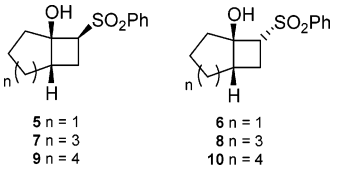
SCHEME 1 [a]



[a] Conditions: (i) LDA, THF, −78 °C; (ii) PhSOCH=CH_2 (bolus addition), −10 °C, 10 min, dark; (iii) aq NH_4Cl.

CHART 1

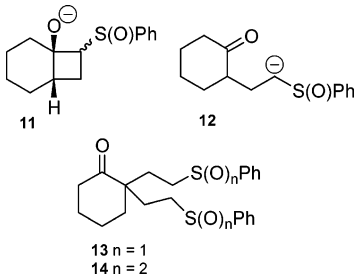


tion, structuralaspects of selected sulfonylbicyclo[*n*.2.0]-alkanols were reported.[15] The previous work[13−15] has demonstrated that this novel cyclization methodology has potential scope using the one methodology for the convergent construction of complex fused ring systems containing a bicyclo[*n*.2.0]alkan-1-ol with bridgehead hydroxyl group. In the present work, we investigate the formation of sulfinylbicyclo[4.2.0]octan-1-ols **1**−**3** from the lithium enolate of cyclohexanone with (±)-phenyl vinyl sulfoxide, as the representative example. By investigating how bicyclo[4.2.0]octan-1-ols might form, further synthetic applications toward important natural products and other synthetic intermediates may be realized.

Results and Discussion

Thermodynamic Control. In previous work we had shown that, within a 24 h time course experiment,[14] the ratio of sulfinylbicyclooctanols **1**−**3** to the monoalkylated ketone **4** decreased from 91:9 at 15 min reaction time, with the monoalkylated ketone **4** being the only product at 24 h. Likewise, increased reaction temperature promoted the formation of the monoalkylated ketone **4**.[14] This suggested that the bicyclooctanol anion(s) **11**, which upon protonation gives sulfinylbicyclooctanols **1**−**3**, is the kinetic product and the monoalkylated anion **12**, which upon protonation gives the monoalkylated ketone **4**, is the thermodynamic product. Presently, we carried out the reactions of the lithium and potassium enolates of cyclohexanone with phenyl vinyl sulfoxide under conditions of forcing thermodynamic control to confirm the absence of sulfinylbicyclooctanols **1**−**3** derived from these conditions. A potassium enolate was chosen in addition

CHART 2



as the counterion-oxygen bond has more ionic character compared to lithium enolates.[16] The lithium and potassium enolates of cyclohexanone were treated with phenyl vinyl sulfoxide in *tert*-butyl alcohol solvent using the appropriate *t*-butoxide as base, at room temperature for a longer reaction time (1.5 h). Monoalkylated ketone **4** (23%) and dialkylated ketone **13** (17%) were obtained from the lithium enolate and dialkylated ketone **13** (57%) from the potassium enolate. The identity of the dialkylated ketone **13** was confirmed upon oxidation with MCPBA to the dialkylated sulfonyl ketone **14** (Chart 2).[17] The sulfinylbicyclooctanols **1**−**3** were not detected in the product mixture. As a result of the more ionic character of the potassium−oxygen bonding, equilibration is promoted and the dialkylated ketone **13** obtained. Further exploration of the reaction conditions for the formation of sulfinylbicyclooctanols **1**−**3** was carried out.

Reaction Lighting. Photochemical methods of cyclobutane formation are well-known[18] but generally do not involve an enolate as reactant. One exception is the photochemical [2 + 2] cycloaddition between aluminum enolates and phenyl vinyl sulfoxide.[19] The lithium enolate of cyclohexanone and phenyl vinyl sulfoxide were reacted under normal laboratory lighting in THF (transmittance range >220 nm), in the dark, and with irradiation[20] (Table 1) from a quartz tungsten halogen lamp (150 W, wavelength range 240−2700 nm), using a standard Pyrex reaction vessel (transmittance range >280 nm). A further experiment using irradiation from a quartz tungsten halogen lamp and a quartz reaction vessel (transmittance range >200 nm) was performed. All yields are based on conversion of nonvolatile phenyl vinyl sulfoxide rather than cyclohexanone, which was often lost during evaporative workup. The reaction between the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide requires cleavage of carbon−carbon double bonds. The bond dissociation energy for carbon−carbon double bonds is typically 427 kJ/mol, and under photochemical conditions this would require a wavelength of 250 nm.[21] Competing photochemically initiated reaction of phenyl vinyl sulfoxide with itself was considered unlikely. From the results in Table 1, minor variations in the ratio of

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TABLE 1. Variation in Lighting Conditions for Reaction between the Lithium Enolate of Cyclohexanone and Phenyl Vinyl Sulfoxide under Standard Conditions[a]

		yield (%)						
entry	conditions	**1**	**2**	**3**	**4**	yield (%) **1**−**4**	PVS(O)[b] (%)	product ratios 1:2:3
1	dark[c]/Pyrex[d]	21.5 ± 1.5	38 ± 6	5 ± 3	10.5 ± 6.5	75 ± 3.5	3 ± 2	31−37:59:4−11
2[f]	lab[e]/Pyrex[d]	13.5 ± 1.5	23.5 ± 3.5	3.5 ± 1.5	24.0 ± 4	64 ± 5	2.5 ± 4.5	31−34:55−61:5−11
3	*hν*[g]/Pyrex[d]	14.3 ± 1.3	26.5 ± 4.5	3 ± 1	20.5 ± 5.5	64 ± 1	6 ± 1	31−35:59−61:5−8
4	*hν*[g]/quartz[h]	12.5 ± 1.5	22 ± 6	5 ± 2	19.5 ± 1.5	59 ± 7	6.4 ± 4.7	31−32:47−62:7−21

[a] Standard reaction conditions: lithium enolate of cyclohexanone (0.085 M) generated from LDA, dropwise addition of phenyl vinyl sulfoxide over 20 s at −10 °C, 10 min reaction time, in THF. Results are from duplicate runs (entries 1, 3, 4) and triplicate runs (entry 2) with average values ± variation indicated. [b] PVS(O) = recovered phenyl vinyl sulfoxide. [c] Light excluded from reaction for total reaction time. [d] Pyrex reaction vessel. [e] Laboratory lighting on reaction for total reaction time. [f] Runs were carried out with 1.0 or 1.1 equiv of LDA or 1.0 equiv of diisopropylamine/butyllithium. [g] Irradiation of reaction by quartz tungsten halogen lamp (150 W) for total reaction time. [h] Quartz reaction vessel.

TABLE 2. Variation in Solvent for Reaction between the Lithium Enolate of Cyclohexanone and Phenyl Vinyl Sulfoxide under Standard Conditions[a]

			yield (%)						
entry	solvent	$E_T(30)$	**1**	**2**	**3**	**4**	yield (%) **1**−**4**	PVS(O)[b] (%)	product ratios 1−3:4
1	DME	38.2	17	29	5	11	62	10	82:18
2[c]	THF	37.4	13.5 ± 1.5	23.5 ± 3.5	3.5 ± 1.5	24 ± 4	64 ± 5	2.5 ± 4.5	60:40 ± 2:2
3[d]	diethyl ether	34.6	14.5 ± 0.5	15 ± 4	0.5 ± 0.5	29.5 ± 7.5	59.5 ± 4.5	4 ± 4	51:49 ± 2:2
4	hexane	30.9	6	10	0	45	61	7	26:74
5	HMPA[e] THF		11	10	0	31	52	0	40:60

[a] Standard reaction conditions: lithium enolate of cyclohexanone (0.085 M) generated from LDA, dropwise addition of phenyl vinyl sulfoxide over 20 s at −10 °C, 10 min reaction time. [b] PVS(O) = recovered phenyl vinyl sulfoxide. [c] Triplicate runs, entry 2, Table 1. [d] Duplicate runs. [e] 4.0 equiv.

sulfinylbicyclooctanols **1**:**2**:**3** (Table 1, entries 1−4) and product yields were observed. A slight enhancement of the yields of sulfinylbicyclooctanols **1** and **2** and the overall product yield was observed under dark reaction conditions (entry 1, Table 1). The overall conversion of phenyl vinyl sulfoxide within experimental variations (entries 1−4, Table 1) did not significantly change. The use of alternative light sources and the addition of sensitizers were not explored. The remaining studies were carried out using normal laboratory lighting as a result of technical ease.

Solvent. The lithium enolate of cyclohexanone and phenyl vinyl sulfoxide were reacted in solvents of varying polarity ($E_T(30)$[22]), namely, DME, THF, diethyl ether, and hexane, under standard conditions (entries1−4, Table 2). The formation of sulfinylbicyclooctanols **1**−**3** was favored in reactions carried out in relatively polar solvents (THF, DME). In addition, sulfinylbicyclooctanol **3** was detected only in these reactions (Table 2, entries 1 and 2). As solvent polarity decreased, the ratio of the sulfinylbicyclooctanols **1**−**3** to the monoalkylated ketone **4** changed from 82:18 in DME to 26:74 in hexane. In a final variation, the lithium enolate of cyclohexanone was generated with LDA in THF containing the chelating agent HMPA[23] (4 equiv because of the low the reaction temperature of −10 °C) and reacted with phenyl vinyl sulfoxide (entry 5, Table 2). Sulfinylbicyclooctanol **3** was not detected in the product mixture. Partial chelation of lithium of the enolate of cyclohexanone by HMPA favored alkylation and thus formation of monoalkylated ketone **4**, as compared to when THF alone was used (entry 2, Table 2).

Enolate Generation. During the course of our studies, competing anionic polymerization of phenyl vinyl sulfoxide[24] was seen to occur in random reactions. These results are not included here. The polymerization was attributed to a catalytic excess of LDA. LDA has been used as an initiator for the anionic polymerization of, for example, methacrylates.[25] Although LDA was titrated with dimethoxybenzyl alcohol[26] or benzyl chloride[27] to accurately determine its concentration, the recovery of phenyl vinyl sulfoxide from most reactions (Tables 1 and 2) indicates a degree of quenching (possibly by water in the reactants) of the 1.1 equiv of LDA used and thus incomplete generation of the lithium enolate of cyclohexanone. In effect, 0.94−0.98 equiv of LDA was employed in these reactions. Notably when 1.0 equiv of LDA was used to generate the lithium enolate of cyclohexanone with predried reagents, the product yields and ratios were comparable to the previous results (entry 2, Table 1). Alternatively, the generation of the lithium enolate of cyclohexanone using methyllithium and excess 1-cyclohexenyloxytrimethylsilane[28] and reaction with phenyl vinyl sulfoxide gave an overall product yield (49%) lower than what had been achieved with LDA (64−75%), but the distribution of sulfinylbicyclooctanols **1**−**3** and the ratio of **1**−**3**:**4** (90:10) was comparable to what had been obtained previously using LDA. The variance of

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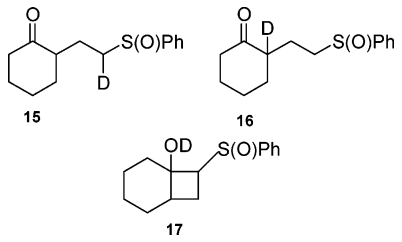
CHART 3



yield was attributed partly to the presence of diethyl ether (7%) as methyllithium was added as a solution in diethyl ether (see solvent study, Table 2). Competing phenyl vinyl sulfoxide polymerization was not observed as the base was not used in excess. The stability of phenyl vinyl sulfoxide toward the excess 1-cyclohexenyloxytrimethylsilane in the absence of base was confirmed independently. Phenyl vinyl sulfoxide and 1-cyclohexenyloxytrimethylsilane (1:1) were stirred in THF at room temperature for 10 min under normal laboratory lighting (Pyrex reaction vessel) and with irradiation from a quartz tungsten halogen lamp (150 W) (quartz reaction vessel), and no reaction occurred in either case. Thus in some experiments the methyllithium method was used, otherwise all reproducible results using LDA are reported.

Deuterium Quench. The lithium enolate of cyclohexanone was generated using methyllithium and 1-cyclohexenyloxytrimethylsilane and reacted with phenyl vinyl sulfoxide at −10 °C for 10 min. The reaction was quenched with deuterated ammonium chloride (20 equiv) in deuterium oxide. Upon workup and purification, sulfinylbicyclooctanols **1** (16%) and **2** (13%) in conjunction with the deuterated monoalkylated ketone **15** (29%) were isolated. Neither the sulfinylbicyclooctanol **3** nor the deuterated monoalkylated ketone **16** was observed (Chart 3). The ^{1}H NMR (400 MHz) spectra of the sulfinyl bicyclooctanols **1** and **2** isolated from the deuterium labeling experiment were identical to those of authentic samples. No changes in the multiplicity of signals in the NMR spectra were observed. Notably, the ^{1}H NMR spectra of isolated **1** and **2** showed signals for hydroxyl protons. This confirmed the presence of the protonated (OH) rather than a deuterated (OD) species such as **17** (Chart 3). It was assumed that the deuterated species **17** formed when the reaction was quenched, but as a result of the high lability of the deuterium label on the oxygen atom, deuterium must have exchanged for hydrogen during workup and chromatography. The slight decrease in formation of bicyclooctanol adducts was attributed to quenching of the reaction with deuterated ammonium chloride in deuterium oxide. The extent of the solvent interactions with the intermediates would be different in the deuterated solvent (D_2O in THF).[29] This would result in a changed energy level for the intermediates and hence changed activation energy of the protonation/deuteration step[30] and apparently slightly promote ring opening of sulfinylbicycloalkanol anion **11** upon quenching.

Unambiguous determination of the structure of the deuterated monoalkylated ketone **15** as a mixture of four diastereomers (see Supporting Information) was carried out using 2D NMR spectra (gCOSY, gHSQC, gHMBC). Key evidence for the position of the deuterium atom was the appearance in the ^{13}C NMR (100 MHz) spectrum of a set of signals for C2′ that were present as 1:1:1 triplets due to coupling to deuterium. The signals for all other carbon atoms in the deuterated monoalkylated ketone **15** were singlets, confirming that the deuterated species was not the alternative structure **16** and that only one deuterium atom had been incorporated. The deuterated monoalkylated ketone **15** was the only compound with a deuterium atom observed in the crude product mixture, as determined by ^{13}C NMR spectroscopy.

Radical Trapping Agent. Attempted trapping of potential radical intermediates by TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical),[31] a radical scavenger, was carried out. TEMPO reacts directly with nonhindered carbon-centered radicals.[32] First, a 1:1 mixture of phenyl vinyl sulfoxide and TEMPO was stirred at room temperature for 20 min, and no reaction occurred. Next, following enolate generation from methyllithium and excess 1-cyclohexenyloxytrimethylsilane, a solution of TEMPO dissolved in phenyl vinyl sulfoxide (1.8:1) was added. Upon workup, analysis by ^{1}H NMR spectroscopy of the crude mixture indicated the presence of phenyl vinyl sulfoxide, 1-cyclohexenyloxytrimethylsilane, some cyclohexanone, sulfinylbicyclooctanols **1**−**3**, and monoalkylated ketone **4** in high mass recovery (92%, see Supporting Information). No peaks attributable to radical trapped products or radical recombination products[33] were present, most of which would be unlikely to decompose under the mild workup conditions. Purification by column chromatography gave recovered TEMPO (52%) (the rest lost to aqueous workup), phenyl vinyl sulfoxide (32%), monoalkylated ketone **4** (10%), and sulfinylbicyclooctanols **1** (24%), **2** (14%), and **3** (3%). No products arising from radical trapping by TEMPO were detected in the column fractions.

(+)-Tolyl Vinyl Sulfoxide. In Scheme 1, the formation of the sulfinylbicyclooctanols **1**−**3** with different relative stereochemistry at sulfur may have resulted from the use of racemic phenyl vinyl sulfoxide. Instead reaction with an optically active electrophile, such as (*R*)-(+)-p-tolyl vinyl sulfoxide **18** was considered. (1*R*,2*S*,5*R*)-(−)-Menthyl-(*S*)-*p*-toluenesulfinate was treated with vinylmagnesium bromide using a modified literature procedure,[34] and upon separation from menthol by column chromatography, (*R*)-(+)-*p*-tolyl vinyl sulfoxide **18** was obtained (57%) in high optical purity. Reaction of the lithium enolate of cyclohexanone (generated from cyclohexanone and LDA) with (*R*)-(+)-*p*-tolyl vinyl sulfoxide **18** under conditions used for phenyl vinyl sulfoxide as

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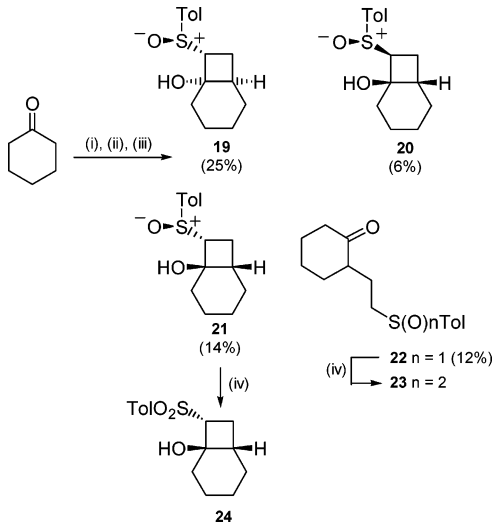
SCHEME 2 [a]



[a] (i) LDA, THF, −78 °C; (ii) (*R*)-(+)-TolS(O)CH=CH$_2$ **18**, −10 °C, 10 min; (iii) NH_4Cl; (iv) MCPBA, $CHCl_3$.

electrophile (dropwise addition of sulfoxide, −10 °C, 10 min, dark, THF, ∼0.08 M) gave, upon purification by chromatography, the tolylsulfinylbicyclooctanols **19** (25%), **20** (6%), **21** (14%), and tolyl monoalkylated ketone **22** (12%) as a 1:1 mixture of diastereomers, epimeric at C2, and in a combined yield of 57% (Scheme 2). The optical rotations obtained for compounds **19**−**22** ($[\alpha]_D = 50-150$) indicated that total racemization had not occurred and implied that some if not all of the stereochemistry at sulfur had been retained and was *R* at sulfur as indicated in Scheme 2. The ee's of **19**−**22** could not be determined by chiral HPLC.[35] The ratio obtained of tolylsulfinylbicyclooctanols **21**:**19**:**20** was 31:56:13 and tolylsulfinylbicyclooctanols **19**−**21**:tolyl monoalkylated ketone **22** was 79:21. The product distribution of tolylsulfinylbicyclooctanols **19**−**20** was consistent of that obtained when phenyl vinyl sulfoxide was used under similar conditions (Table 1, entry 2). Tolyl monoalkylated ketone **22** and tolylsulfinylbicyclooctanol **21** were characterized as the sulfones **23** and **24**, respectively, upon oxidation with MCPBA (Scheme 2).

The tolylsulfinylbicyclooctanols **19**−**21** and tolylsulfonylbicyclooctanol **24** also were characterized by interpretation of spectral data from ^{1}H and ^{13}C 1D NMR and gCOSY, gHSQC, and gHMBC 2D NMR, FT-IR spectroscopy, and mass spectrometry. The connectivity patterns in the NMR spectra were similar to those observed for the corresponding phenylbicyclooctanols **1**−**3**.[13] An important outcome of use of the optically active electrophile was to establish the complete relative configuration of the bicyclooctanol products. X-ray structural determination unambiguously indicated the relative configurations (not the absolute configuration) of tolylsulfinylbicyclooctanols **19** and **20** and tolylsufonylbicyclooctanol **24**[15a] (Figure 1).

In Figure 1, these diagrams each clearly show the *cis* ring junction with the six-membered ring in a chair

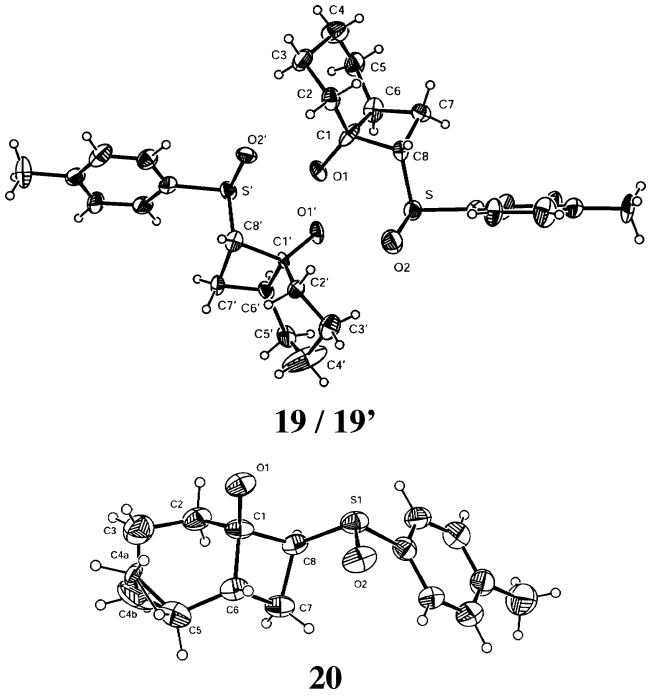


FIGURE 1. ORTEP-3 diagram of the molecular structure of tolylsulfinylbicyclooctanols **19**/**19′** and **20**. Displacement ellipsoids are drawn with 30% probability.

conformation fused to the puckered four-membered ring. For the tolylsulfinylbicyclooctanol **19**, there are two discrete molecules in the asymmetric unit of the unit cell (**19** and **19′**). Disorder in the cyclohexyl ring at C4 is evident in the structure of tolylsulfinylbicyclooctanol **20** (Figure 1). The bond lengths and angles for **19** and **20** are comparable to those recorded previously for the sulfinylbicyclooctanols **2** and **3**.[13] The torsion angles about the C1−C6 ring junction in the tolylsulfinylbicyclooctanols **19**, **19′**, and **20** were −17(1)° (**19**), −19(1)° (**19′**), and −16.6(6)° (**20**) for C7−C6−C1−C8 and −34(2)° (**19**), −34(2)° (**19′**), and −26(1)° (**20**) for C2−C1−C6−C5. Short intermolecular O···O distances are reflective of hydrogen bonding interactions in **19** with O1···O1′ (i), 2.78(1) Å and O1···O2′ (i), 2.69(1) Å ((i) symmetry code $2 - x$, $1/2 + y$, $1 - z$) and in **20** with O1···O2 (ii) 2.738(7) Å; (ii) symmetry code $1/2 - x$, $1 - y$, $1/2 + z$).

Discussion

The sulfinylbicyclooctanols **1**−**3** form on protonation of the sulfinylbicycloalkanol anion **11** as the major product(s) at short reaction time and lower temperature, whereas with a much longer reaction time the sulfinylbicycloalkanol anion **11** ring opens to the monoalkylated anion **12** and gives the monoalkylated ketone **4** as the only product. Similiarly, conditions of protonated solvent and increased temperature promote of the formation of monoalkylated cyclohexanone **4**. Evidence for the anion **12** was obtained by isolation of the deuterated ketone **15** as the only deuterated compound when a deuterium quench of the reaction was used. The absence of the deuterated monoalkylated ketone **16** indicated that under the reaction conditions employed equilibration of the anion **12** did not occur. The percentage contribution arising from ring opening of the bicyclo[4.2.0]octan-1-ol

(35) Chiral HPLC was carried out using a Chiralcel OD-H column, Agilent 1100 series HPLC equipped with a Quat pump and diode array detector. Racemic **2** was used as an appropriate standard for **19**−**22**. Racemic **2** could not be sufficiently resolved, and the optical purity (ee) of **19**−**22** could not be determined.

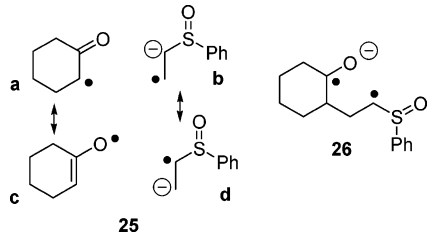
anion **11** versus the direct alkylation of the enolate of cyclohexanone by phenyl vinyl sulfoxide (see **28** below) could not be determined. The monoalkylated anion **12** must be considered the thermodynamic product of the sulfinylbicycloalkanol anion **11** and can thus not be an intermediate toward the formation of the bicycloalkanol anion **11** via an ionic mechanism.

Sulfinylbicyclooctanols **1**−**3** formation could potentially occur via a concerted pathway. Concerted [2 + 2] cycloaddition pathway in cyclobutane formation has been described for a photochemical process[18] and a thermal process involving linear molecules such as ketenes and allenes.[36] In a synchronous or nonsynchronous concerted mechanism for the formation of bicyclooctanols the stereochemistry at sulfur should be preserved in the products. When optically active (*R*)-(+)-*p*-tolyl vinyl sulfoxide **18** was used, total racemization at sulfur did not occur and the formation of epimers at C8 was observed. The generation of a *cis* ring junction in all sulfinylbicyclooctanols **1**−**3** and **19**−**21** was noteworthy. However, the short length of the carbon chain in the phenyl/tolyl vinyl sulfoxide electrophile may preclude attack from the opposite face in a nonsynchronous process and formation of a *trans* ring junction.

Single electron transfer also could provide a route to the sulfinylbicycloalkanolide anion **11**, via either a photochemical or thermal process. Diagnostic criteria for the detection of electron-transfer mechanisms are varied. Spectroscopic methods for the detection of radicals include ESR spectroscopy[37] and CIDNP[38] using NMR spectroscopy. Other criteria include the stereochemical outcomes of the reaction, the formation of radical-derived secondary products, kinetic studies, isotope effects, and the failure of a reaction to conform to a simple linear free energy relationship.[39] Because formation of sulfinylbicyclooctanols **1**−**3** in the reaction between the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide occurs under anhydrous conditions and at low temperature, synthetic methods were chosen to explore for evidence of any free radical intermediates.

The results reported in Table 1 indicate that no consistent trend between reaction lighting conditions and reaction outcome was observed. No significant effects occurred in the distribution and yields of the products when the lighting conditions were altered to promote a photochemical process (entries 3 and 4, Table 1) or when all light sources that would activate a photochemical process were eliminated (entry 1, Table 1). The formation of the sulfinylbicyclooctanols **1**−**3** in the dark excludes any photochemical pathways to the sulfinylbicycloalkanol anion **11**. A thermal electron transfer may be occurring. Electron transfer between the enolate and phenyl vinyl sulfoxide could give rise to the radical/radical anion pair **25**, which could combine in a number of ways. However, the cyclohexanone radical is more likely to be carbon-centered as the enolate of cyclohexanone has been shown

CHART 4



to react in a SET to give 2-phenylcyclohexanone.[40] The rate of radical−radical coupling should occur faster than an ionic process.[41] Thus combination of the radical/radical anion ion pair **25a/25b** is likely to form monoalkylated anion **12** rather than bicycloalkanol anion **11** in a concerted process. Alternatively, electron transfer of the monoalkylated anion **12** could give rise to the species **26** (Chart 4). However, as both of these possible pathways proceed via the monoalkylated anion **12** prior to formation of the sulfinylbicycloalkanol anion **11**, they could be considered unlikely because of the thermodynamic consideration outlined above.

No direct evidence was obtained for any radical intermediates. Attempts to trap any radical intermediates with TEMPO were unsuccessful, and radical trapped products or radical recombination products were not detected. However, radical reactions can be very rapid and radical intermediates may indeed be present. The solvent usually has little effect on free radical reactions,[42] although there are cases where the rate of reaction for trapping a radical is promoted by a more polar solvent.[43] Notably a change in solvent polarity gave significant changes in product distribution (entries 1−4, Table 2). However, addition of the chelating agent HMPA (entry 5, Table 2) diverted the reaction away from the formation of the sulfinylbicycloalkanols **1**−**3**. These results are generally indicative of an ionic process. Sulfinyl-stabilized carbanions, derived from base removal of a proton α to a sulfoxide, are generally assumed to be pyramidal and sp^3-hybridized, where lithium cation−oxygen chelation may control the conformation in THF and retain the stereochemisty at sulfur.[44] Instead a free anion is predominant in the presence of a chelating agent. However, α-lithiosulfoxides anions with increased sp^2-hydridization and with a stronger S−O···Li chelation have been reported.[45]

The results presented herein can be accounted for by a variety of mechanisms. Two more likely possible mechanisms are presented in Scheme 3. Radical combination of the radical/radical ion pair **29** (tautomeric to the radical/radical anion pair **25**) or addition of the enolate to phenyl vinyl sulfoxide via the complex **27** (arising from coordination of the lithium enolate with phenyl vinyl sulfoxide) might provide the intermediate

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(40) Scamehorn, R. G.; Hardacre, J. M.; Lukanich, J. M.; Sharpe, L. R. *J. Org. Chem.* **1984**, *49*, 4881.

(41) For example: (a) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1993**, *58*, 6476. (b) Garst, J. F.; Hines, J. B., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 6443.

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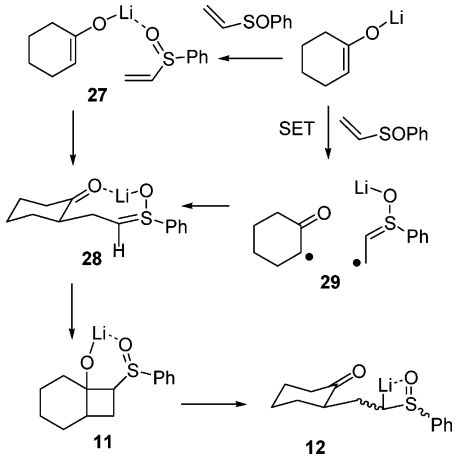
SCHEME 3



28. In both **27** and **29** the lithium cation is predisposed to be associated with the sulfoxide oxygen and provide the intermediate **28** by which racemization at carbon (C8 in the bicycloocatanol) and retention at sulfur can occur. The species **28** is a thermodynamically distinct species from the anion **12** as the result of solvation and ion-pairing effects. Ring closure of **28** to the bicyclooctanol anion **11** could be facilitated as the lithium cation is available to make the carbonyl oxygen part of the chelation cage. Ring opening (a slow process) of the bicyclooctanol anion **11** to the monoalkylated anion **12** then occurs to produce a racemic anion, a consequence of the intermediate **28**, which upon quenching with deuterium gives racemic deuterated ketone **15**. The lithium cation now has a stronger C···Li interaction in the sulfoxide anion **12** and is diverted away from chelation with the carbonyl group and from ring closure as a result. Clearly the addition of HMPA alters the reactivity of the enolate and chelation effects of the reaction intermediates as does the solvent used.

Conclusions

Although there is more than one possible pathway to **11**, whether **11** arises from more than one pathway could not be determined. Likewise no compelling evidence allowed us to unambiguously determine a pathway for formation of **11**. However, the combination of results obtained, such as sensitivity of bicyclooctanol formation to solvent used and presence of a chelation agent (HMPA) and epimerization at C8, suggests an intermediate (for example **28**) is present prior to formation of bicycloalkanol anion **11**. Bicycloalkanol anion **11** then slowly ring opens to the sp^3-hybridized monoalkylated anion **12**. With some understanding in place, further synthetic applications of the cyclization reaction toward the construction of more complex systems and manipulation of the sulfoxide functional group can now proceed.

Experimental Section

The general experimental instrumentation and procedures and procedure for oxidation of sulfoxides have been described elsewhere.[13] Optical rotations were measured on a Jasco P-1020 Polarimeter. Bicyclo[*n*.2.0]octan-1-ols **1**−**3**,[13] **5**,[15a] **6**,[14] **7**,[15a] **8**,[14] **9**,[15a] **10**,[14] **24**,[15a] and monoalkylated ketone **4**[13,46] have been characterized previously.

^{1}H NMR Crude Product Analysis and Determination of Percentage Composition. The crude product mixtures were dried under high vacuum and freeze-dried, and the mass of the crude product was determined. The ^{1}H NMR spectra were obtained using $CDCl_3$ as solvent. A D_2O exchange was performed on all samples, and the ^{1}H NMR (400 MHz) spectrum was obtained. Integration of the baseline resolved peaks at δ 3.29, 3.14, 3.05, 2.95, and 6.18, for sulfinylbicyclooctanols **1**, **2**, **3**, monoalkylated ketone **4** and unreacted phenyl vinyl sulfoxide, respectively, was used to calculate the percentage composition of these components from the integral of the total crude mixture. The percentages reported are calculated yields based on starting moles of phenyl vinyl sulfoxide.

Lithium Enolate of Cyclohexanone and Phenyl Vinyl Sulfoxide in *tert*-Butyl Alcohol. Cyclohexanone (0.50 g, 0.53 mL, 5.10 mmol) was added to a solution of butyllithium (1.4 M, 0.4 mL, 0.52 mmol) in *tert*-butyl alcohol (5 mL). Phenyl vinyl sulfoxide (0.85 g, 0.75 mL, 5.60 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was neutralized by dropwise addition of glacial acetic acid and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to give the crude product mixture as a yellow oil (1.17 g). The crude product mixture was separated by silica column chromatography (ethanol/DCM 3:97). Fraction 1 contained the monoalkylated ketone **4** (292 mg, 23%). Fraction 2 contained a diastereomeric mixture of 2,2-bis[2′-(phenylsulfinyl)ethyl]-cyclohexanone **13** (340 mg, 17%) isolated as an almost colorless oil: FTIR (neat) 2932, 1701, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44−2.74 (m, 16H, aliphatic), 7.35−7.60 (m, 10H, C_6H_5); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 20.18, 25.39, 25.84, 26.03, 26.37, 26.50, 26.57, 26.62, 35.73, 35.91, 36.12, 38.53, 38.59, 38.65, 49.96, 50.13, 50.17, 50.27, 50.74, 50.77, 123.73, 123.82, 129.06, 130.86, 142.82, 143.07, 213.02; MS (ESI+ve) 425 (MNa^+, 100%). Oxidation of the dialkylated ketone **13** (155 mg, 0.39 mmol) with 3-chloroperoxybenzoic acid (57%, 236 mg, 0.78 mmol) in $CHCl_3$ (7 mL) gave the crude product as an almost colorless oil (202 mg). The oil was analyzed by ^{1}H NMR (400 MHz) spectroscopy and was determined to contain the dialkylated sulfonyl ketone **14** (80%) with the remainder attributable to 3-chlorobenzoic acid and ethyl acetate. Purification by silica column chromatography (ethyl acetate 100%) gave 2,2-bis[2′-(phenylsulfonyl)ethyl]cyclohexanone **14** as a white solid: mp 123−124 °C (ethyl acetate); FTIR (neat) 2931, 1702, 1306, 1147 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55−1.63 (m, 2H, 2 × H3), 1.63−1.76 (m, 4H, 2 × H4, 2 × H5), 1.81 (ddd, 2H, $J_{1',1'} = 14$, $J_{1',2'} = 12$, $J_{1',2'} = 5$ Hz, 2 × H1′), 1.93 (ddd, 2H, $J_{1',1'} = 14$, $J_{1',2'} = 12$, $J_{1',2'} = 4$ Hz, 2 × H1′), 2.23 (t, 2H, $J = 6.5$ Hz, 2 × H6), 2.77 (ddd, 2H, $J_{2',2'} = 14$, $J_{2',1'} = 12$, $J_{2',1'} = 4$ Hz, 2 × H2′), 2.93 (ddd, 2H, $J_{2',2'} = 14$, $J_{2',1'} = 12$, $J_{2',1'} = 5$ Hz, 2 × H2′), 7.48−7.58 (m, 4H, *m*-C_6H_5), 7.58−7.67 (m, 2H, *p*-C_6H_5), 7.80−7.88 (m, 4H, *o*-C_6H_5); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 20.2 (C4), 26.5 (C1′, C5), 35.8 (C3), 38.6 (C6), 49.6 (C2), 50.8 (C2′), 127.8 (*o*-C_6H_5), 129.3 (*m*-C_6H_5), 133.9 (*p*-C_6H_5), 138.6 (*i*-C_6H_5), 212.4 (C1); MS (ESI+ve) 441 (MLi^+, 100%); HRMS calcd for $C_{22}H_{26}O_5S_2$ 434.12217, found 434.12217. Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 60.80; H, 6.03. Found: C, 61.06; H, 6.16.

Example of Procedure of Variation in Lighting: With Lighting from a Tungsten Halogen Lamp (150 W) in a Quartz Reaction Vessel. The lithium enolate of cyclohexanone, generated from LDA (titrated against benzyl chloride) (2.25 M, 1.25 mL, 2.80 mmol) and cyclohexanone (0.25 g, 0.26 mL, 2.55 mmol) in THF (30 mL), was allowed to warm to −10 °C, and phenyl vinyl sulfoxide (0.39 g, 0.34 mL, 2.55 mmol) was added dropwise over 20 s, while light from a tungsten

(46) Montgomery, J.; Overman, L. *J. Org. Chem.* **1993**, *58*, 6476.

halogen lamp (150 W) was applied at 10 cm from the reaction vessel. The reaction mixture was stirred for 10 min under this lighting, and the temperature was maintained at −10 °C during this time. The reaction was quenched (aqueous NH_4Cl, saturated) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude product mixture was obtained as an amber oil ((a) 570 mg; (b) 449 mg). The percentage composition of the major products, as determined by analysis of the crude product mixture by ^{1}H NMR (400 MHz) spectroscopy, was monoalkylated ketone **4** ((a) 21%; (b) 18%), sulfinylbicyclooctanol **1** ((a) 14%; (b) 11%), sulfinylbicyclooctanol **2** ((a) 28%; (b) 16%), sulfinylbicyclooctanol **3** ((a) 3%; (b) 7%), and phenyl vinyl sulfoxide ((a) 11%; (b) 1.7%).

Example of Procedure of Variation in Solvent: In Dimethoxyethane. The lithium enolate of cyclohexanone was generated from LDA (titrated against benzyl chloride) (2.25 M, 1.25 mL, 2.80 mmol) and cyclohexanone (0.25 g, 0.26 mL, 2.55 mmol) in anhydrous DME (30 mL). The solution was allowed to warm to −10 °C, and phenyl vinyl sulfoxide (0.39 g, 0.34 mL, 2.55 mmol) was added dropwise over 20 s. The reaction mixture was stirred for 10 min, and the temperature was maintained at −10 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (519 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was monoalkylated ketone **4** (11%), sulfinylbicyclooctanol **1** (17%), sulfinylbicyclooctanol **2** (29%), sulfinylbicyclooctanol **3** (5%), and phenyl vinyl sulfoxide (10%).

Quench with Deuterated Ammonium Chloride in Deuterium Oxide. The lithium enolate of cyclohexanone was generated as outlined above using methyllithium (1.4 M, 1.60 mL, 2.24 mmol) and 1-cyclohexeneyoxytrimethylsilane (0.46 g, 0.52 mL, 2.70 mmol) in THF (10 mL). The solution was allowed to warm to −10 °C, and phenyl vinyl sulfoxide (0.34 g, 0.30 mL, 2.24 mmol) added dropwise over 20 s. The reaction was stirred for 10 min, and the temperature was maintained at −10 °C during this time. The pale yellow solution was quenched with deuterated ammonium chloride (2.79 g, 48.50 mmol) in deuterium oxide (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to give the crude product mixture as an amber oil (466 mg). The crude product mixture was separated by silica column chromatography (2-propanol/DCM 4:96). Fraction 1 contained 2-[2′-^{2}*H*-2′-(phenylsulfinyl)ethyl]cyclohexanone **15** as a mixture of four diastereomers (a−d) and as a white solid (161 mg, 29%): mp 79−80 °C (ether); FTIR (KBr) 2931, 1700, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23−1.43 (m, 4H, 1 × H3a−d). 1.47−1.70 (m, 12H, 1 × H1′a−d, 1 × H4a−d, 1 × H5a−d), 1.70−1.93 (m, 6H, 1 × H1′b, 1 × H1′c, 1 × H4a−d), 1.93−2.12 (m, 10H, 1 × H1′a, 1 × H1′d, 1 × H3a−d, 1 × H5a−d), 2.13−2.39 (m, 10H, H2b, H2c, 2 × H6a−d), 2.39−2.51 (m, 2H, H2a, H2d), 2.62−2.69 (m, 1H, H2′d), 2.77−2.86 (m, 2H, H2′b, H2′c), 2.86−2.94 (m, 1H, H2′a), 7.40−7.49 (m, 12H, *m*- and *p*-C_6H_5a−d), 7.53−7.59 (m, 8H, *o*-C_6H_5a−d); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (C1′b, C1′c), 22.9 (C1′a, C1′d), 24.9, 25.0 (C4a−d), 27.8, 27.9 (C5a−d), 34.3, 34.4 (C3a−d), 42.0 (C6a−d), 49.2 (C2a, C2d), 49.7 (C2b, C2c), 53.9 (t, $J_{C,D}$ 21, C2′b, C2′c), 54.7 (t, $J_{C,D}$ 21, C2′a), 54.8 (t, $J_{C,D}$ 21, C2′d), 123.9, 124.0 (*o*-C_6H_5a−d), 129.07, 129.10 (*m*-C_6H_5a−d), 130.77, 130.84 (*p*-C_6H_5a−d), 143.3 (*i*-C_6H_5b, *i*-C_6H_5c), 143.9 (*i*-C_6H_5a, *i*-C_6H_5d), 212.0 (C1b, C1c), 212.1 (C1a, C1d); MS (ESI+ve) 274 (MNa^+, 100%); HRMS calcd[47] for $C_{14}H_{17}O_2DSH^+$ requires 252.11675, found 252.11579. Anal. Calcd for $C_{14}H_{17}DO_2S$: C, 66.90; H, 7.62. Found: C, 66.92; H, 7.47. Fraction 2 contained sulfinylbicyclooctanol **2** (73 mg, 13%). Fraction 3 contained sulfinylbicyclooctanol **1** (88 mg, 16%). Incorporation of deuterium for nonexchangeable protons was not evident by analysis by ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectroscopy of the sulfinylbicyclooctanols **1** and **2**.

In the Presence of 2,2,6,6-Tetramethyl-1-piperidinyloxy Free Radical (TEMPO). Under an atmosphere of nitrogen, methyllithium (1.4 M, 0.80 mL, 1.12 mmol) in ether was added dropwise to a solution of 1-cyclohexeneyloxytrimethylsilane (0.26 g, 0.30 mL, 1.54 mmol) in anhydrous THF (10 mL). The temperature was maintained between −40 and −30 °C during this time. The colorless solution was stirred for 20 min and warmed −10 °C. 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical (TEMPO) (0.17 g, 1.9 mmol) dissolved in phenyl vinyl sulfoxide (0.16 g, 0.14 mL, 1.05 mmol) and THF (0.5 mL) was added dropwise over 20 s. The reaction was stirred for 10 min, and the temperature was maintained at −10 °C during this time. The translucent red solution was quenched and worked up as described above. The crude product mixture was obtained as a dark amber oil (397 mg) and contained 1-cyclohexenyloxytrimethylsilane, which was removed by further evaporation under reduced pressure. The crude product mixture was separated by silica column chromatography (ether 100% followed by ethyl acetate 100%), and two major fractions were obtained. Fraction 1 contained recovered TEMPO (89 mg, 52% recovery based on moles of starting TEMPO). Fraction 2 (209 mg), as determined by analysis by ^{1}H NMR (400 MHz) spectroscopy, contained phenyl vinyl sulfoxide (32%), the monoalkylated ketone **4** (10%), sulfinylbicyclooctanol **1** (24%), sulfinylbicyclooctanol **2** (14%), and sulfinylbicyclooctanol **3** (3%).

Reaction with (*R*)-(+)-*p*-Tolyl Vinyl Sulfoxide 18. The lithium enolate of cyclohexanone generated from LDA (∼2.18 M, 1.30 mL, 2.83 mmol) and cyclohexanone (0.25 g, 0.26 mL, 2.55 mmol) in THF (30 mL) at −78 °C was allowed to warm to −10 °C and was placed in the dark. (*R*)-(+)-*p*-Tolyl vinyl sulfoxide **18** (0.42 g, 2.55 mmol) was added dropwise over 20 s, and the reaction mixture was stirred for 10 min. The temperature was maintained at −10 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (454 mg). Purification by silica column chromatography (2-propanol/DCM 4:96) gave three fractions. Fraction 1 contained the monoalkylated tolyl sulfoxide **22** and bicyclooctanol tolyl sulfoxide **20** (135 mg). Further purification of fraction 1 by silica column chromatography (ether 100%) and gave bicyclooctanol tolyl sulfoxide **20** (41 mg, 6%) and 2-{2′-[(4-methylphenyl)sulfinyl]ethyl}cyclohexanone **22** as a 1:1 mixture of diastereomers, (82 mg, 12%). Fraction 2 contained bicyclooctanol tolyl sulfoxide **19** (167 mg, 25%). Fraction 3 contained bicyclooctanol tolyl sulfoxide **21** (94 mg, 14%).

(1*R*S_C,6*S*R_C,8*S*R_C,*R*S_S)-8-(4-Methylphenyl)sulfinylbicyclo[4.2.0]octan-1-ol **20**, purified by semipreparative HPLC (methanol/DCM 3:97), was a white solid: mp 141−143 °C (ether); $[\alpha]^{24}_D$ +153.9 (*c* 0.063, MeOH); FTIR (KBr) 3297, 2925, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20−1.37 (m, 3H, 1 × H5, 1 × H3, 1 × H4), 1.37−1.70 (m, 5H, 1 × H2, 1 × H3, 1 × H4, 1 × H5, 1 × H7), 1.88−1.98 (m, 1H, 1 × H2), 2.23 (ddd, 1H, $J_{7,8\alpha}$ 4, $J_{7,6\beta}$ 10, $J_{7,7}$ 13, 1 × H7), 2.37 (s, 3H, CH_3), 2.57−2.68 (m, 1H, H6β), 3.02 (ddd, 1H, $J_{8\alpha,6\beta}$ 1, $J_{8\alpha,7}$ 4, $J_{8\alpha,7}$ 8, H8α), 3.35 (s, 1H, OH), 7.25−7.30 (m, 2H, *m*-C_6H_4), 7.39−7.45 (m, 2H, *o*-C_6H_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6 (C7), 20.8 (C3, C4), 21.4 (CH_3), 24.7 (C5), 35.6 (C2), 43.4 (C6), 67.1 (C8), 74.7 (C1), 124.2 (*o*-C_6H_4), 129.7 (*m*-C_6H_4), 138.1 (*p*-C_6H_4), 140.9 (*i*-C_6H_4); MS (ESI+ve) 287 (MNa^+, 100%). Anal. Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.63. Found: C, C, 68.23; H, 7.73.

2-{2′-[(4-Methylphenyl)sulfinyl]ethyl}cyclohexanone **22** as a 50:50 mixture of diastereomers, was an off-white wax (82 mg, 12%): $[\alpha]^{24.1}_D$ +52.8 (*c* 0.075, MeOH); FTIR (Nujol) 1713, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ∗ denotes second diastereomer) δ 1.27−1.44 (m, 2H) 1.52−1.72 (m, 5H) 1.78−1.98 (m, 5H) 1.98−2.14 (m, 4H) 2.17−2.38 (m, 6H) (4 × H2, 4

(47) As the ^{1}H and ^{13}C NMR spectra of **11** indicated incorporation of one deuterium atom, it was assumed that the protonated species $C_{14}H_{17}O_2DSH^+$ had been generated during the ionization process of HRMS.

× H3, 4 × H4, 4 × H5, 4 × H6, 2 × H1′), 2.38 (s, 6H, 2 × CH_3), 2.43−2.56 (m, 1H, 1 × H2′), 2.70 (ddd, 1H, $J_{2',1'}$ 5, $J_{2',1'}$ 10, $J_{2',2'}$ 13, H2′*), 2.77−2.98 (m, 2H, 1 × H2′*, 1 × H2′), 7.26−7.32 (m, 4H, *m*-C_6H_4), 7.44−7.52 (m, 4H, *o*-C_6H_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 22.0, 23.1 (C1′), 25.0 (C4), 27.9 (C5), 34.3, 34.4 (C3), 42.1 (C6), 49.3, 49.8 (C2), 54.4, 55.2 (C2′), 124.0 (*o*-C_6H_4), 129.7 (*m*-C_6H_4), 140.2 (*p*-C_6H_4), 141.1 (*i*-C_6H_4), 211.9 (C1); MS (ESI+ve) 287 (MNa^+, 100%). Sulfinylmonoalkylated ketone **22** was characterized as the sulfonylmonoalkyated ketone **23**.

(1*SR*$_C$,6*RS*$_C$,8*RS*$_C$,*RS*$_S$)-8-(4-Methylphenyl)sulfinylbicyclo-[4.2.0]octan-1-ol **19** recrystallized as a white solid: mp 121−122 °C (ether); $[\alpha]^{23.7}_D$ +129.8 (*c* 0.172, MeOH); FTIR (KBr) 3373, 2923, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26−1.40 (m, 2H, 1 × H4, 1 × H5), 1.40−1.52 (m, 3H, 1 × H4, 2 × H3), 1.54−1.63 (m, 1H, 1 × H2), 1.67−1.82 (m, 3H, 1 × H2, 1 × H5, 1 × H7), 1.98 (ddd, 1H, $J_{7,8\alpha}$ 4, $J_{7,6\beta}$ 10, $J_{7,7}$ 13, 1 × H7), 2.38 (s, 3H, CH_3), 2.71−2.81 (m, 1H, H6β), 3.13 (ddd, 1H, $J_{8\alpha,6\beta}$ 1, $J_{8\alpha,7}$ 4, $J_{8\alpha,7}$ 8, H8α), 4.12 (s, 1H, OH), 7.26−7.31 (m, 2H, *m*-C_6H_4), 7.52−7.58 (m, 2H, *o*-C_6H_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8 (C3), 21.1 (C4), 21.4 (C7), 21.6 (CH_3), 25.0 (C5), 36.8 (C2), 41.5 (C6), 66.1 (C8), 76.6 (C1), 125.1 (*o*-C_6H_4), 129.8 (*m*-C_6H_4), 139.6 (*p*-C_6H_4), 141.5 (*i*-C_6H_4); MS (ESI+ve) 271 (MLi^+, 100%). Anal. Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.63; S, 12.13. Found: C, 68.03; H, 7.87; S, 11.92.

(1*RS*$_C$,6*SR*$_C$,8*SR*$_C$,*RS*$_S$)-8-(4-Methylphenyl)sulfinylbicyclo-[4.2.0]octan-1-ol **21**[48] recrystallized as a white solid: mp 168−170 °C (ether); $[\alpha]^{23.3}_D$ +80.6 (*c* 0.172, MeOH); FTIR 3386, 2932, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.54 (m, 5H) 1.54−1.68 (m, 3H) 2.03−2.32 (m, 3H) (2 × H2, 2 × H3, 2 × H4, 2 × H5, H6β, 2 × H7), 2.38 (s, 3H, CH_3), 3.25 (dd, 1H, $J_{8\beta,7}$ 8, $J_{8\beta,7}$ 10, H8β), 3.73 (s, 1H, OH), 7.25−7.30 (m, 2H, *m*-C_6H_4), 7.45−7.51 (m, 2H, *o*-C_6H_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 20.1, 21.3, 21.4, 23.3 (C3, C4, C5, C7, CH_3), 31.7 (C2), 38.5 (C6), 69.4 (C8), 74.5 (C1), 124.2 (*o*-C_6H_4), 129.9 (*m*-C_6H_4), 139.1 (*p*-C_6H_4), 141.5 (*i*-C_6H_4); MS (ESI+ve) 271 (MLi^+, 100%). Anal. Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.63; S, 12.13. Found: C, 68.18; H, 7.87; S, 12.38.

Crude monoalkylated tolyl sulfone **23** was obtained from tolyl monoalkylated ketone **22** (56 mg, 0.21 mmol) as a white solid (45 mg, 76%). Recrystallization gave 2-{2′-[(4-methylphenyl)sulfonyl]ethyl}cyclohexanone **23** as a white solid: mp 96−98 °C (ether); FTIR (KBr) 1713, 1302, 1147 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (dddd, 1H, $J_{3ax,4eq}$ 3.5, $J_{3ax,2ax}$ 13, $J_{3ax,4ax}$ 13, $J_{3ax,3eq}$ 13, H3ax), 1.50−1.72 (m, 3H, 1 × H1′, 1 × H4, 1 × H5), 1.80−1.88 (m, 1H, 1 × H4), 1.92−2.12 (m, 3H, 1 × H1′, H3eq, 1 × H5), 2.19−2.37 (m, 2H, 2 × H6), 2.42 (s, 3H, CH_3), 2.42−2.52 (m, 1H, H2ax), 3.08 (ddd, 1H, $J_{2',1'}$ 6, $J_{2',1'}$ 10, $J_{2',2'}$ 14, 1 × H2′), 3.24 (ddd, 1H, $J_{2',1'}$ 6, $J_{2',1'}$ 10, $J_{2',2'}$ 14, 1 × H2′), 7.30−7.36 (m, 2H, *m*-C_6H_4), 7.72−7.79 (m, 2H, *o*-C_6H_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (CH_3), 23.2 (C1′), 25.1 (C4), 27.9 (C5), 34.3 (C3), 42.1 (C6), 48.9 (C2), 54.0 (C2′), 127.9 (*o*-C_6H_4), 129.8 (*m*-C_6H_4), 136.1 (*p*-C_6H_4), 144.5 (*i*-C_6H_4), 211.6 (C1); MS (ESI+ve) 303 (MNa^+, 100%). Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19; S, 11.43. Found: C, 64.22; H, 7.28; S, 11.36.

Crude tolylsulfonylbicyclooctanol **24** was obtained from tolylsulfinylbicyclooctanol **21** (71 mg, 0.27 mmol) as a white solid (60 mg, 79%). Purification by silica column chromatography (ethyl acetate/hexane 50:50) gave (1*RS*,6*SR*,8*RS*)-8-(4-methylphenyl)sulfonylbicyclo[4.2.0]octan-1-ol **24** as a white solid, mp 139−141 °C (ether), the spectral data of which were identical to those of the tolylsulfonylbicyclooctanol **24**, described previously.[15a]

Crystal Structure Determination of 8-Tolylsulfinylbicyclo[4.2.0]octanols 19 and 20. Data Collection, Structure Solution, and Refinement. Unique data sets were measured at 295 K within $2\theta_{max} = 50°$ (**19**), 55° (**20**) using a Rigaku AFC7R four circle diffractometer (ω-2θ scan mode, monochromated Mo Kα radiation, $\lambda = 0.71069$ Å) yielding N independent reflections, N_o with $I > 2\sigma(I)$ being considered "observed". The structures were solved by direct methods and refined by full matrix least squares refinement on $|F|$. Anisotropic thermal parameters were refined for non-hydrogen atoms; (x, y, z, U_{iso})$_H$ were included and constrained at estimated values with the exception of the hydroxyl protons, which were not located from difference Fourier maps. Weights derivative of $w = 1/[\sigma^2(F)]$ were employed. Conventional residuals R, R_w on $|F|$ at convergence are quoted; statistical weights were employed. Neutral atom complex scattering factors were employed, computation used the teXsan crystallographic software package for Windows version 1.06 (Molecular Structure Corporation),[49] ORTEP-3,[50] and PLATON.[51]

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre CCDC nos. 242235 − 242236.

Crystal Data. (1*RS*$_C$,6*SR*$_C$,8*SR*$_C$,*SR*$_S$)-8-(4-Methylphenyl)-sulfinylbicyclo-[4.2.0]octan-1-ol **19** recrystallized from ether: $C_{15}H_{20}O_2S_1$, $M = 264.4$, monoclinic, space group $P2_1$, $a = 9.99(1)$, $b = 11.47(1)$, $c = 13.073(5)$ Å, $\beta = 108.77(4)°$, $U = 1417(2)$ Å^3, $Z = 2$, $D_c = 1.24$ g cm^{-3}, $\mu = 2.21$ cm^{-1}. Crystal size: 0.40 × 0.30 × 0.25 mm^3, $N = 2643$, $N_o = 1104$; $R = 0.058$, $R_w = 0.051$.

(1*RS*$_C$,6*SR*$_C$,8*SR*$_C$,*RS*$_S$)-8-(4-Methylphenyl)sulfinylbicyclo-[4.2.0]octan-1-ol **20** recrystallized from ether. $C_{15}H_{20}O_2S_1$, $M = 264.4$, orthorhombic, space group $P2_12_12_1$, $a = 9.237(2)$, $b = 25.003(6)$, $c = 6.240(2)$ Å, $U = 1441.2(6)$ Å^3, $Z = 4$, $D_c = 1.22$ g cm^{-3}, $\mu = 2.17$ cm^{-1}. Crystal size: 0.30 × 0.30 × 0.25 mm^3, $N = 2151$, $N_o = 931$; $R = 0.056$, $R_w = 0.054$.

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Supporting Information Available: Standardization of LDA; full description of experiments; discussion of assignment of the NMR spectra of deuterated ketone **15**; listing of purity data for known compounds **1**−**4**, **16**, and **24**; and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(48) The stereochemistry at sulfur was assigned by correlation of spectra with the corresponding phenyl sulfinylbicyclooctanols **1**−**3**.

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