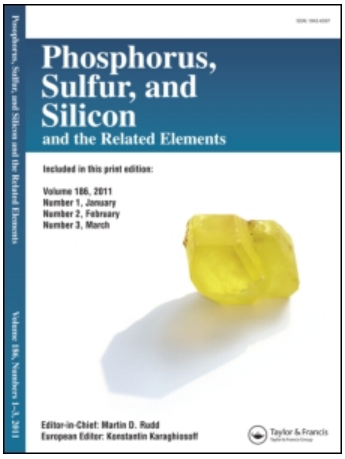

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Utilization of Sulfoximines in the Synthesis of Optically Pure Substances

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UTILIZATION OF SULFOXIMINES IN THE SYNTHESIS OF OPTICALLY PURE SUBSTANCES

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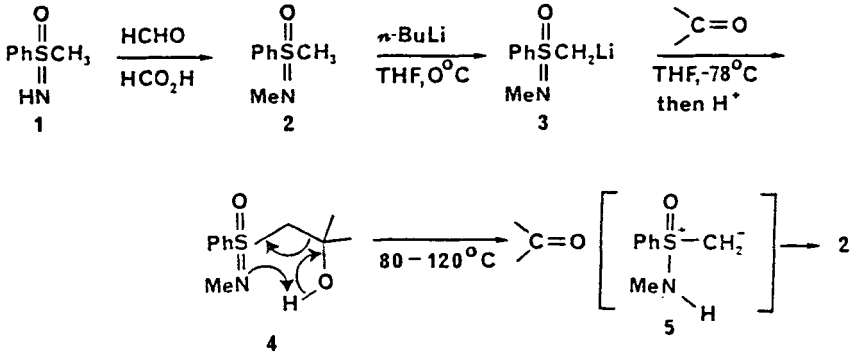
ABSTRACT Optically active β-hydroxysulfoximines, obtained by addition of the lithio reagent 3 to carbonyl compounds may serve as suitable intermediates for the optical resolution of ketones, methylenations of ketones with optical resolution, enantioface-selective cyclopropanation of enones and synthesis of optically active dihydroxy cycloalkanones. Several examples of syntheses of natural products by this methology are given.

S-Methyl-S-phenylsulfoximine (1) can be readily resolved using 1o-camphorsulfonic acid [1,2]. From the d-acid the salt of (+)-(S)-1 is obtained pure by recrystallization. The Clarke-Eschweiler procedure using formaldehyde and formic acid provides a very effective method for the transformation of 1 to N,S-dimethyl-S-phenylsulfoximine (2) [1,3]. Compound 2 in tetrahydrofuran is rapidly deprotonated with butyllithium to provide N-methylphenylsulfonimidoylmethyllithium (3). Lithio reagent 3 is an excellent nucleophile particularly with respect to addition to carbonyl compounds [4,5]. The addition reaction occurs with a wide range of aldehydes and ketones in the temperature range of -78 to 25°C to provide β-hydroxysulfoximines 4 in high yield (Scheme 1).

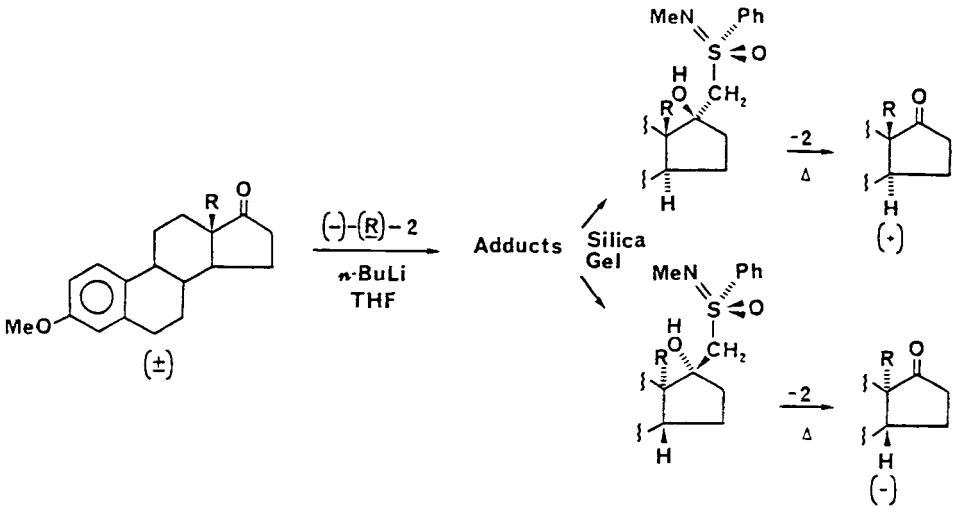
We have found that β-hydroxysulfoximines are thermally unstable and revert to the starting carbonyl compound and sulfoximine in the temperature range of 8o to 12o°C [5,6]. The reversion is probably facilitated by the transfer of the OH proton to the sulfoximine nitrogen

such that carbon-carbon bond cleavage occurs with the ylide 5 as the leaving group [1]. The ylide self-quenches by tautomerization to the starting sulfoximine (Scheme 1).



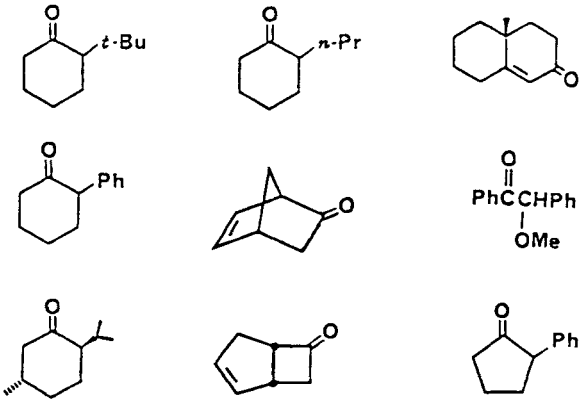
Scheme 1

The non-stereoselective addition of optically pure 2 (as the lithio reagent 3) to a chiral dl-ketone will result in four optically active diastereomeric adducts. Thermolysis of each optically pure adduct should lead to optically pure ketone and the regenerated and recyclable sulfoximine reagent. Generally the separation of four adducts would not be considered as practical for a ketone resolution. Ideally complete diastereoselectivity in the addition reaction should prevail as it would result in only two diastereomers and considerably simplify the separation problem, e.g., Scheme 2. The two



Scheme 2

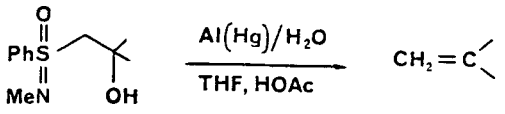
classes of ketones that are most likely to exhibit good diastereoface selectivity are substituted cycloalkanones and open-chain ketones bearing chelating substituents nearby the C=O. Indeed, the above chemistry has been found to be an interesting and novel method for the resolution of variety of ketones a sampling of which is shown in Scheme 3 [5,6].



Scheme 3

In all cases of substituted cyclohexanones which we have examined, two major adducts and a trace of a third diastereomer were produced in the addition reaction. A significant advantage inherent in the method is the rapidity with which the ultimate success of a resolution of a ketone can be predicted. Chromatographic examination (thin-layer chromatography or HPLC on silica gel) of a small-scale reaction mixture resulting from the addition of racemic 2 to racemic ketone, optically pure 2 to racemic ketone (assuming that complete mutual kinetic resolution does not obtain), or racemic 2 to an optically pure ketone will reveal the number and separability of the various diastereomers. The method has reciprocity and a number of ketones, particular l-menthone have been found useful to resolve dl-2. This method complements the camphorsulfonic acid resolution method noted above. We have often used the menthone method to bring the material (after methylation) recovered from the mother liquors of the sulfonic acid resolution up to optical purity[7].

β-Hydroxysulfoximines obtained by the addition of 3 to aldehydes and ketones, undergo reductive elimination to yield alkenes upon treatment with aluminum/mercury amalgam in a mixture of THF, water and acetic acid (Scheme 4) [4,8]. The combination of the

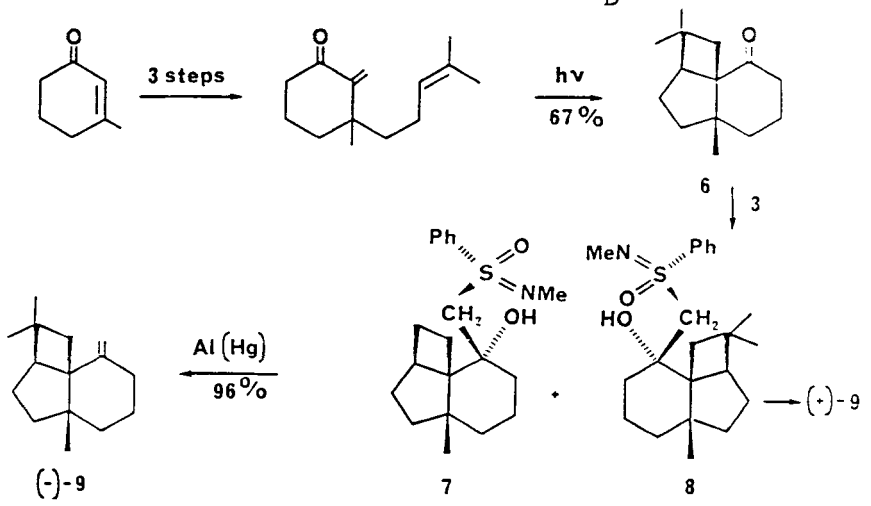


Scheme 4

chromatographic separation of optically active β-hydroxysulfoximine diastereomers with the reductive elimination has resulted in methodology which leads to ketone methylenation with optical resolution. The technique was the keystone in the total synthesis of the ginseng sesquiterpene (-)-β-panasinsene (9) and its enantiomer (Scheme 5)[9]. Several points concerning this synthesis are noteworthy. The ketone 6 had been previously found by McMurry and Choy to be "inert to methylenetriphenylphosphorane in DMSO" [10].

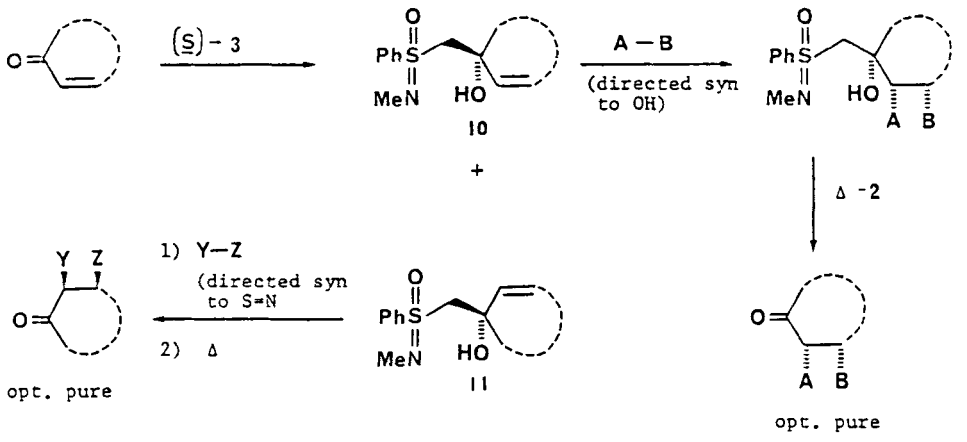
In a reaction exhibiting remarkable diastereoselectivity, the addition of dl-3 to dl-ketone 6 gave a 30:1 mixture of dl-7 and its diastereomer dl-8 (opposite relative configuration at S). The (S)-reagent 3 kinetically selects a single carbonyl face of the (-)-enantiomer of 6 and the (R)-3 selects the same carbonyl face of (+)-6 to give dl-7 as the major product. Addition of (S)-3 to dl-ketone 6 resulted in a ca. 1:1 mixture of optically-active 7 and 8 which were readily separated by flash chromatography. Treatment of (+)-7 with Al/Hg resulted in β-panasinsene (9) with $[\alpha]_D^{25}$ -27.7°; (-)-8 gave the

unnatural (+)-β-panasinsene with $[\alpha]_D^{25}$ + 29.7°.



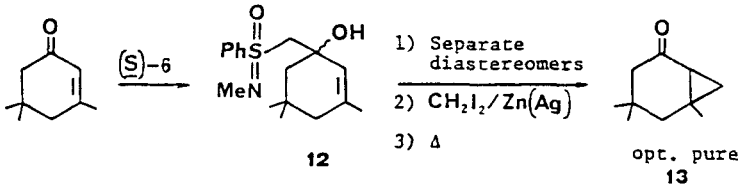
Scheme 5

The addition of optically pure 2 as the lithio reagent 3 to prochiral enones or the diastereoface selective addition to racemic chiral enones results in the formation of two optically active diastereomeric adducts, e.g., 1o and 11 (Scheme 6). In such adducts we envisioned that the hydroxyl group and/or the sulfoximine nitrogen might serve to control diasteroface selectivity in addition reactions to the remaining carbon-carbon double bond. Combining this diastereoface selectivity of the addition with a subsequent thermal reversion of the sulfoximine addition would result, in effect, in enantioface-controlled additions to the carbon-carbon double bond of the original enone (Scheme 6).



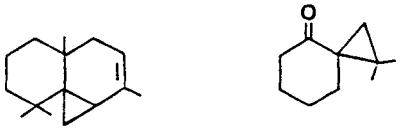
Scheme 6

For our first test of this concept, the Simmons-Smith cyclopropanation reaction was chosen as it has been well documented to be directed by oxygen coordination [11]. Treatment of the individual diastereomeric isophorone/sulfoximine adducts 12 with diiodomethane/zinc (silver) in refluxing diethyl ether followed by thermolysis resulted in the enantiomeric cyclopropyl ketones 13 with $[\alpha]^{25}_{D}$ + 16o.6° and -164° (Scheme 7). This methodology has been applied to the synthesis of (-)- and (+)-thujopsene (14) and a variety of other optically pure cyclopropyl ketones, e.g., 15[12].



12 13

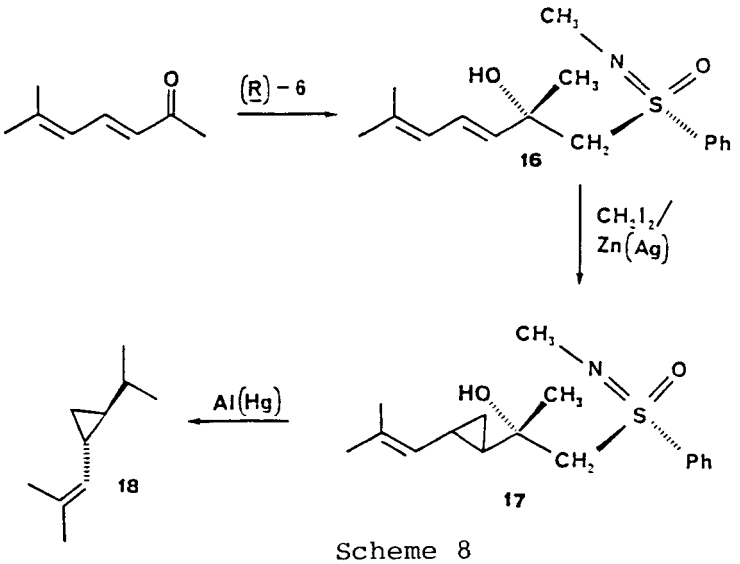
Scheme 7



14 15

Scheme 8 outlines the total synthesis of the non-head-to-tail monoterpene, (-)-rothrockene (18) [13]. In this sequence it is interesting to note the multifaceted role of sulfoximine chemistry. Incorporation of the β-hydroxysulfoximine moiety allowed for the resolution of the precursor (16), regio- and diastereoface selectivity in the cyclopropanation which selectively formed 17, crystallographic determination of the absolute configuration of 17 (and hence 18) by relating carbon stereochemistry to the known absolute stereochemistry at sulfur, and introduction of the final carbon-carbon double bond in 18.

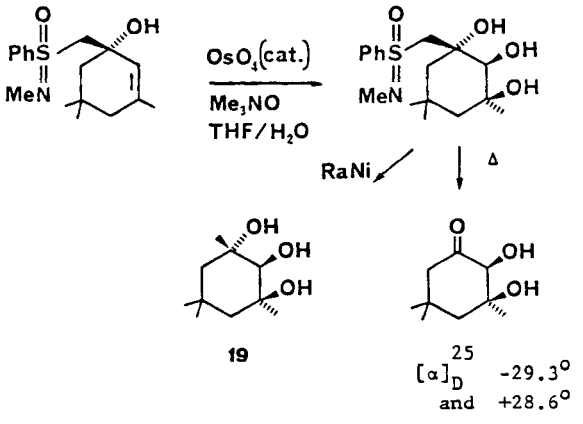
Osmium tetroxide is known to reversibly form adducts with basic ligands such as pyridine and quinuclidine [14]. We anticipated that the methylimino group of adducts 10 and 11 would provide, by "chelation control", diastereoface selection in the osmylation of the adja-



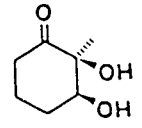
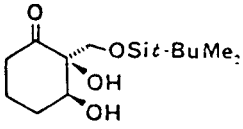
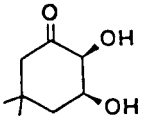
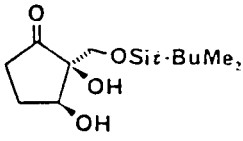
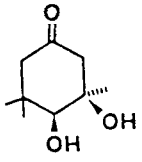
Scheme 8

cent carbon-carbon double bond. Furthermore, the "anti-periplanar" effect of the allylic hydroxyl group should provide a synergistic enhancement of the diastereoface selectivity [15,17]. The overall result would be a novel optical activation method involving directed osmylation and thermal reversal of the sulfoximine addition to afford optically pure dihydroxy cycloalkanones and the recyclable resolving agent 2. Again, the optically pure adducts of isophorone and 2 were chosen for initial study (Scheme 9) [16]. Treatment of the individual diastereomers in water/THF solutions containing trimethylamine N-oxide dihydrate (1.5 equiv) with solutions of osmium tetroxide (5 mol%) [18] in THF afforded, in each case, a single triol. Desulfurization of each triol provided a materialwhich exhibited ten resonances in the decoupled ^{13}C NMR spectrum and four methyl singlets in the ^{1}H NMR spectrum, consistent with the unsymmetrical structure 19. The optically active cis-hy-

droxylated sulfoximine adducts undergo clean thermal elimination of the sulfoximine in refluxing solvent (2-butanol, toluene, or xylene) to provide optically pure dihydroxy cycloalkanones. A selection of compounds prepared by this technique is shown in Scheme 10. Of particular note are the successes obtained with a 3-cyclohexenone substrate (homoallylic oxidation) and the cyclopentenone substrate. In the latter case preparation of the diols shown represents formal total syntheses of both optical isomers of the antibiotics pentenomycin I and II since Smith and co-workers [19] have successfully converted racemic material to these substances. To date, attempts to extend this oxidation methodology to the preparation of enantiomerically pure acyclic diol ketones have not been successful [20].



Scheme 9

Product	$[\alpha]_D^{25}$	Product	$[\alpha]_D^{25}$
	+ 0.7° - 0.8°		-52.3° +51.2°
	-21.2° +21.6°		+35.2° -34.7°
	-24.2° +24.0°		

Scheme 10

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