2.15 (s, 6 H), 4.5 (m, 1 H, CH); MS/EI m/e (relative intensity) 115 (M, 10), 77 (100), 55 (70).

Acknowledgment. We thank Dr. Yu-Chu Yang of CRDEC for helpful discussions. This work was supported by grants from the National Science Foundation (CHE 8800471) and the US Army CRDEC. We thank Mr. Mark V. Haley of CRDEC for performing the toxicological studies.

Registry No. **2a**, 139131-28-5; **2b**, 139131-29-6; **2c**, 139131-30-9; **2d**, 139131-31-0; **3a**, 28519-50-8; **3b**, 139131-32-1; **5**, 139131-33-2; **7b**, 65332-44-7; **10a**, 139131-34-3; **10c**, 139131-35-4; **10d**, 139131-36-5; **11a**, 824-79-3; **11b**, 824-80-6; **13a**, 139131-37-6; **13b**, 139131-38-7; **13d**, 139131-39-8; **14c**, 139131-40-1; **14d**, 139131-41-2; **16**, 94143-77-8; VX, 50782-69-9; 2-(dimethylamino)ethyl chloride hydrochloride, 4584-46-7; 2-(diisopropylamino)ethyl chloride hydrochloride, 4261-68-1; *p*-fluorobenzenesulfonyl chloride, 349-88-2.

Supplementary Material Available: ^{1}H NMR spectra of hydrochlorides **10a**, **10c**, and **10d**, vinyl sulfides **14c** and **14d**, and nitrone **16** (7 pages). Ordering information is given on any current masthead page.

Asymmetric Oxidation of Simple Selenides to Selenoxides in High Enantiopurity. Stereochemical Aspects of the Allyl Selenoxide/Allyl Selenenate Rearrangement

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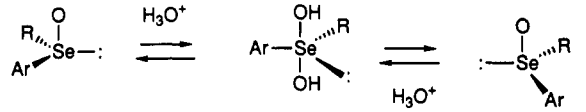
Received January 14, 1992

For the first time simple alkyl aryl selenoxides of high enantiomeric purity (90–95% ee) and well-defined stereochemistry are available via the asymmetric oxidation of selenides using (+)- or (−)-*N*-(phenylsulfonyl)-(3,3-dichlorocamphoryl)oxaziridine [**4**, [3,3-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spiro[bicyclo[2.2.1]heptane-2,3′-oxaziridine]]]. These nonracemic selenoxides, which are more stable in solution than in the solid state, exhibit high configurational stability as long as acid and moisture are excluded. Complete racemization occurs within minutes on addition of trace amounts of acid and water. The asymmetric oxidation of (*E*)- and (*Z*)-aryl cinnamyl selenides **11** and **12** with oxaziridine (+)-**4** affords optically active 1-phenyl allyl alcohol (**15**) via a concerted [2,3] sigmatropic selenoxide–selenenate rearrangement. The extent of 1 → 3 chirality transfer (41–62% ee) as well as the endo/exo transition state geometry is highly dependent on the structure of the allylic selenide.

Until recently, simple chiral selenoxides were little studied, being first reported by us in 1983.[1,2] This is in contrast to chiral sulfoxides which have been known since the mid-1920s[3] and have played pivotal roles in studies of the origins of molecular recognition and in asymmetric synthesis.[4] Optically active diaryl selenoxides have been prepared by chromatographic resolution on chiral columns (12–66% ee),[5,6] and by oxidation with *tert*-butyl hypochlorite in the presence of (−)-2-octanol (1.0% ee).[7] Oxidation of prochiral selenides with enantiopure *N*-sulfonyloxaziridines (up to 13%)[2] and with the Sharpless reagent (7–40% ee)[8] gives enantiomerically enriched alkyl aryl selenoxides. Microbial oxidation of selenides to selenoxides, however, failed.[9] Resolution of racemic selenoxides by complexation with chiral diols and by kinetic resolution with chiral sulfonamides (6–10% ee)[1] has also been described.[10] In addition, diastereomeric selenoxides have been prepared by oxidation of steroidal[11] and nonracemic [2.2]paracyclophane-substituted selenides.[12]

The principal difficulty in studying and preparing chiral selenoxides in high enantiomeric purity is their configurational lability. In earlier studies we demonstrated that chiral alkyl arylselenoxides racemize in the presence of moisture via the formation of an achiral hydrate **1** which



1

is strongly acid catalyzed.[1,2] Bulky ortho substituents were shown to slow the rate of racemization by sterically inhibiting the formation of **1**. Subsequent studies by Shimizu et al. confirmed these results and established that the rate-limiting step is protonation of the selenoxide oxygen.[13] These same workers succeeded in preparing enantiomerically pure (−)-4-(methoxycarbonyl)phenyl 2,4,6-triisopropylphenyl selenoxide, which is air-stable, by fractional

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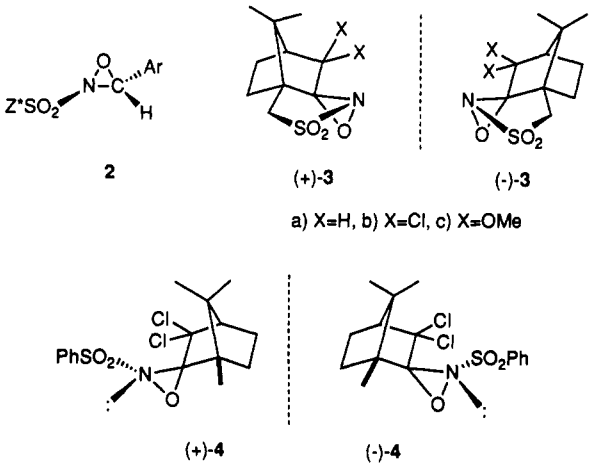
crystallization of the diastereomeric menthyl ester followed by removal of the chiral auxiliary.[14] The absolute configuration of this selenoxide was established by X-ray crystallographic analysis of the diastereomer.

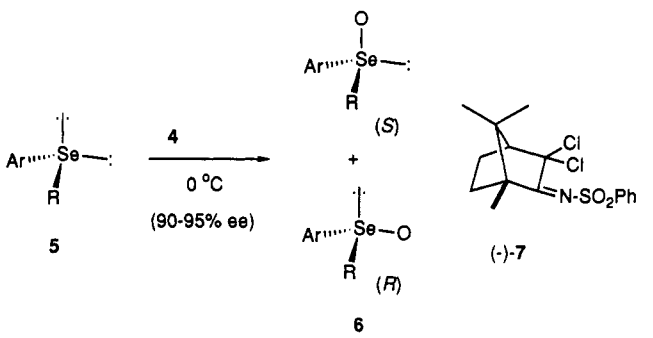
Selenoxides, like sulfoxides, can also racemize by a pyramidal inversion mechanism. Activation barriers ($\Delta G^{\ddagger}$) of 61 to better than 77 kJ mol^{-1} have been reported for the racemization of diastereomeric diaryl selenoxides using ^{77}Se NMR.[15] Interestingly, bulky ortho substituents increased the barriers to racemization. Activation barriers for alkyl aryl and diaryl sulfoxides are considerably higher, 150–180 kJ mol^{-1}.[16]

It is clear from the preceding discussion that to prepare simple selenoxides in high enantiomeric purity a procedure needs to be not only highly enantiospecific but also free of moisture and acid. The method of choice for the synthesis of nonracemic selenoxides, at least in principal, is the asymmetric oxidation of prochiral selenides to selenoxides using enantiopure *N*-sulfonyloxaziridines **2–4**.[17] These reagents are an important class of oxidants that are finding increased utility in asymmetric synthesis. Since they are aprotic and neutral reagents, oxidations can be carried out under rigorously anhydrous conditions. The configuration of the oxaziridine three-membered ring controls the product stereochemistry so that either enantiomer is available simply by choice of the antipodal reagent. Oxaziridines of type **2** epoxidize nonfunctional-



ized *trans*-alkenes with stereoselectivities up to 94% ee.[18] The (camphorylsulfonyl)oxaziridine derivatives **3** are much better than either types **2** or **4** for the hydroxylation of prochiral enolates to α-hydroxy carbonyl compounds with ee's often better than 95%.[19] The most efficient of these reagents for the enantioselective oxidation of prochiral sulfides to sulfoxides is *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine [**4**, [3,3-dichloro-1,7,7-trimethyl-

Scheme I[a]



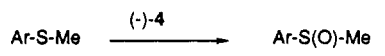
[a] Key: (a) Ar = Ph, R = Me. (b) Ar = 2,4,6-triisopropylphenyl, R = Me. (c) Ar = 2,4,6-triisopropylphenyl, R = Et. (d) Ar = 2,4,6-triisopropylphenyl, R = *p*-MeOPhCH$_2$.

2′-(phenylsulfonyl)spiro[bicyclo[2.2.1]heptane-2,3′-oxaziridine]]]. This reagent not only gives high ee's (90–95%) but is also remarkably general.[20] This paper describes the application of **4** for the synthesis and study of alkyl aryl selenoxides in high enantiomeric purity (>90%).

Results

Asymmetric Oxidation of Selenides to Selenoxides. Asymmetric oxidations were accomplished by treatment of the selenide **5** with 1 equiv of oxaziridines **3** or **4** at −60 or 0 °C (Scheme I). Oxidation of methyl phenyl selenide (**5a**) was complete within 1 min whereas the bulkier alkyl triisopropylphenyl selenides **5b–d** required several hours. In order to ensure that oxidation was carried out under anhydrous conditions solvents were distilled from P_2O_5 into a receiver containing anhydrous K_2CO_3 and stored over 3-Å molecular sieves. Omitting the K_2CO_3 treatment resulted in complete racemization of the selenoxides, presumably because of acid impurities. The enantiomeric purity of the selenoxides **6** was determined by using the chiral shift reagent Eu(fod)$_3$ or (+)-(trifluoromethyl)-9-anthrylethanol. These results, summarized in Table I, indicate that oxidant **4** affords these selenoxides in better than 90% ee whereas reagent **3** gave lower selectivities.

Results for the asymmetric oxidation of methyl *p*-tolyl sulfide (**8a**, Ar = *p*-tolyl) and methyl 2,4,6-triisopropylphenyl sulfide (**8b**, Ar = 2,7,6-triisopropylphenyl), to the sulfoxides **9** by (−)-**4** are recorded for comparison in Table I. Analogous to the corresponding selenoxides **6a** and **6b**, sulfoxides **9a** and **9b** were obtained in better than 95% ee. However, a major difference between sulfides and selenides is that the ee's for the latter were solvent-dependent exhibiting higher stereoselectivity in the nonpolar solvents such as CCl_4 (Table I, entries 5 and 6 and 12 and 13). Another difference is that selenides are oxidized much faster than sulfides. For example, **5a** and **5b** were oxidized in <1 min and 4 h, respectively, compared to 4 and 16 h for **8a** and **8b**. These differences can be ascribed to the longer C–Se (1.98 Å) vs C–S (1.81 Å) bond lengths which reduce steric interactions in the transition state resulting in faster rates of oxidation for the selenides.



Isolation and Properties of Chiral Selenoxides. Selenoxides **6b–d** were isolated in good yield without racemization by removing the solvent under vacuum and

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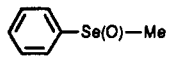
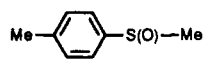
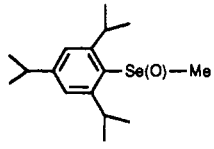
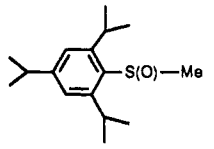
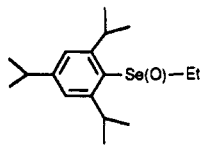
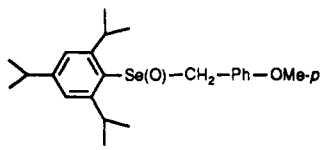
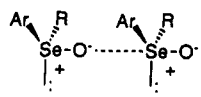
(20) Davis, F. A.; Thimma Reddy, R.; Han, W. *J. Am. Chem. Soc.* **1992**, *114*, 1428.

Table I. Asymmetric Oxidation of Alkyl Aryl Selenides to Selenoxides Using (Camphorylsulfonyl)oxaziridines at 0 °C

entry	selenoxide	solvent	oxaziridine	% ee by NMR[a] (config)[b] [time (h)]	isolated % ee[a] [% yield][c]	$[\alpha]^{25}_{D}$ ($CHCl_3$)	CD (λ_{ext}, nm)
1	 **6a**	$CHCl_3$	(+)-**3a**	10 (*S*) [*d*]	0 (–) [68]		
2		$CHCl_3$	(–)-**4**	>95 (*S*) [*d*]	15 (*S*)[e] [70]		
3		CCl_4	(–)-**4**	94 (*S*) [*d*]	10 (*S*) [74]		
4		CH_2Cl2	(–)-**4**	64 (*S*) [*d*]	12 (*S*) [65]		
5	 **9a**	$CHCl_3$	(–)-**4**		79 (*S*) [90]		
6		CCl_4	(–)-**4**		>95 (*S*) [90]	–139.0° (*c*, 1.6)[f]	–241
7	 **6b**	$CHCl_3$	(+)-**3a**	84 (*S*) [1.5]	70 (*S*)[g] [72]	–47.4° (*c*, 1.1)	–280
8		$CHCl_3$	(–)-**3a**	82 (*R*) [1.5]	69 (*R*)[g] [65]	+45.4° (*c*, 1.2)	+280
9		$CHCl_3$	(–)-**4**	>95 (*S*) [1.5]	85 (*S*) [85]	–57.0° (*c*, 1.1)	–280
10		CCl_4	(–)-**4**	94 (*S*) [2]	83 (*S*) [75]		
11		CH_2Cl_2	(–)-**4**	93 (*S*) [2]	83 (*S*) [81]		
12	 **9b**	$CHCl_3$	(–)-**4**		81 (*S*) [90]		
13		CCl_4	(–)-**4**		>95 (*S*) [90]	–182.4° (*c*, 2.3)[f]	–268
14	 **6c**	$CHCl_3$	(+)-**3a**	68 (*S*) [1.5]	54 (*S*) [74]		
15		$CHCl_3$	(–)-**4**	91 (*S*) [2]	86 (*S*) [68]	–37.7° (*c*, 0.62)	–275
16	 **6d**	$CHCl_3$	(+)-**3a**	72 (*S*) [1.5]	68 (*S*) [65]		
17		$CHCl_3$	(=)-**4**	95 (*S*) [2]	87 (*S*) [60]	+139.0° (*c*, 0.62)	–295

[a] Ee's determined using $Eu(fod)_3$. [b] Proposed configuration based on active-site model. [c] Isolate yield after chromatography. [d] Oxidation complete in <1 min. [e] Configurations determined using Pirkle's solvent (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. [f] In acetone. [g] CD spectrum used to determine configurations.

extracting into *n*-pentane. This procedure removes greater than 95% of the sulfonimine **7**. Analytically pure samples were obtained by chromatography on basic alumina, but some racemization occurred (Table I). Methyl phenyl selenoxide (**6a**) could not be isolated in a similar manner due to its partial insolubility in *n*-pentane, and samples contained ca. 20% of the sulfonimines. Although we had reported earlier the isolation of **6a** by sublimation (ca. 9% ee),[2] attempts to reproduce this result consistently failed. Crystalline selenoxides **6b–d** were configurationally stable for a few days at 0 °C but slowly racemized on standing for several weeks. Even though ethyl 2,4,6-triisopropylphenyl selenoxide (**6c**) is prone to syn elimination it was stable under these conditions. Interestingly, **6b–d** racemized much faster in the solid state than in solution where they were stable for more than 1 month. We speculate that intermolecular association of the polar Se–O bond moieties may be responsible, i.e., **10**. As previously noted addition of trace amounts of *p*-toluenesulfonic acid resulted in the complete racemization of these selenoxides within minutes.[1,2]



10

(*S*)-(–)-Methyl 2,4,6-triisopropylphenyl selenoxide (**6b**) on refluxing in benzene for 18 h did not racemize. However, in the higher boiling solvents such as toluene (–)-**6b** racemized within 4 h. Lack of reproducibility, undoubtedly due to its moisture sensitivity, precluded attempts to obtain meaningful rates of racemization.

Selenoxide Absolute Configuration. Enantioselective oxidations of sulfides to sulfoxides with **4** revealed that the configuration of the oxaziridine ring controls the absolute stereochemistry of the product which can be predicted using simple steric arguments.[20] The mechanisms of chiral recognition for the asymmetric oxidation of sulfides to sulfoxides and selenides to selenoxides are likely to be related since the mechanisms of oxidation involving an S_N2-type substitution are analogous.[21,22] Transition-state structure **TS-1** is predicted to be of lower energy than **TS-2** because there are fewer nonbonded interactions when the small group of the selenide (R_S–Se–R_L) fits into the molecular cleft defined by the chlorine atom and phenyl sulfonyl group of (–)-**4** (Figure 1).[20] Thus, (–)-**4** affords, nearly exclusively, (*S*)-selenoxides (Table I). Similar arguments can be applied to oxidations by (+)- and (–)-**3a**. The assignments are further supported by the fact that sulfoxides **9a** and **9b**, of known absolute configuration, have circular dichroism (CD) spectra similar to selenoxides **6b–c** (Table I).

(21) Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C.; Bach, R. D. *J. Org. Chem.* **1986**, *51*, 4240.
(22) Bach, R. D.; Coddens, B. A.; McDouall, J. J. W.; Schlegel, H. B.; Davis, F. A. *J. Org. Chem.* **1990**, *55*, 3325.

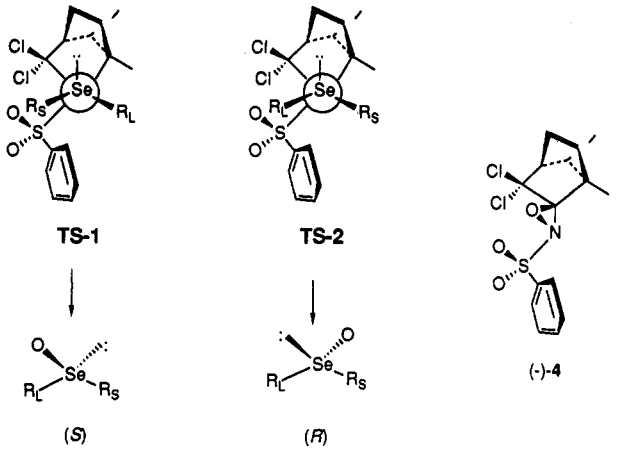
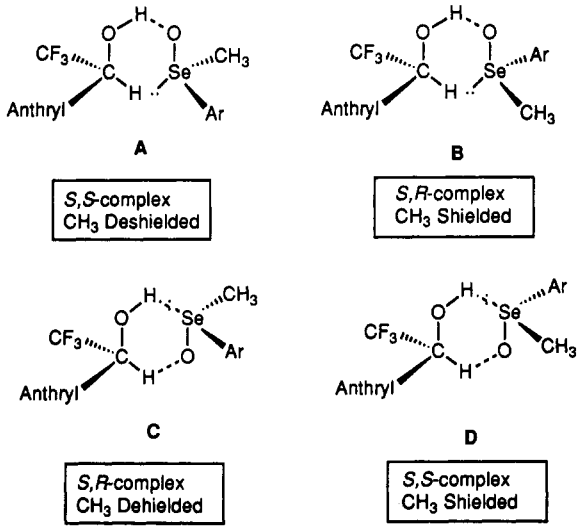


Figure 1.

Scheme II



Pirkle and co-workers have shown that ^{1}H NMR spectra of sulfoxide enantiomers in the presence of nonracemic perfluoroalkylcarbinols are nonequivalent.[23] These chiral solvating reagents can be used not only to determine the ee's of a substrate but also to assign the absolute configuration. The latter application is based on a postulated two-point interaction, stabilizing short-lived diastereomeric solvates A and B (Scheme II). The primary interaction is thought to be a hydrogen bond between the hydroxy group of the alcohol with the sulfinyl (seleninyl) oxygen, with a secondary interaction between the carbinyl hydrogen and the sulfinyl (seleninyl) electron pair. The observed spectral nonequivalence arises from differential shielding of the enantiomeric methyl protons by the aromatic ring of the fluoro alcohol in solvates A and B.

In the presence of (*S*)-(−)-2,2,2-trifluoro-1-(10-methyl-9-anthryl)ethanol the methyl protons of (*S*)-methyl phenyl selenoxide (**6a**) and (*S*)-methyl *p*-tolyl sulfoxide (**9a**) are deshielded by δ 0.06 ppm compared to the *R* enantiomer as predicted by models A and B (Scheme II). However, application of this chiral solvating reagent to (*S*)-methyl 2,4,6-triisopropylphenyl selenoxide and sulfoxide, **6b** and **9b**, respectively, predicts the wrong *R* configuration; i.e., the methyl protons are shielded by δ 0.1 ppm compared to the *R* enantiomer. Since the absolute configurations of these compounds are well established by application of the transition-state model (Figure 1) and the CD spectra, the fault must lie with the solvate model. In Pirkle's idealized sulfoxide–chiral solvating reagent model steric effects, which were never explicitly addressed, are undoubtedly important in determining the conformational preference. In order to accommodate our results we suggest that unfavorable steric interactions between the large 2,4,6-triisopropylphenyl and anthryl groups destabilizing diastereomeric solvates A and B such that hydrogen bonding between the hydroxy alcohol and the selenyl (sulfinyl) lone pairs become dominant favoring models C and D (Scheme II). As first pointed out by Pirkle, our results further emphasize the fact that generalized correlations between the senses of nonequivalence observed in chiral substrate–chiral solvent reagent systems and absolute configurations are unwarranted unless the solvent–solute interactions are well understood.[24]

Stereochemistry of the Allyl Selenoxide/Allyl Selenenate Rearrangement. The reversible allyl sulfenate–sulfoxide [2,3] sigmatropic rearrangement, widely used in the synthesis of many natural products, involves the stereospecific transfer of oxygen from sulfur to carbon (Scheme III, Se = S).[25] Of particular concern in this rearrangement is the degree of 1 → 3 transfer of chirality. Mislow[26] and others[27] have established that chirality transfer depends on the relative energies of the diastereomeric exo and endo transition states which are interconvertible by rotation about the C–Se (C–S) and C–C bonds. The higher specificity exhibited by acyclic *Z* sulfoxides compared to *E* sulfoxides was attributed to a less favorable steric bias for the exo transition state in the latter. For example, (*R*)-(*E*)-sulfoxide **13**, (Se = S, R^1 = H, $R^2 = C_5H_{11}$) affords (*R*)-(−)-1-octen-3-ol in 29% ee while rearrangement of (*R*)-(*Z*)-**13** (Se = S, $R^1 = C_5H_{11}$, R^2 = H) affords the allylic alcohol in better than 80% ee.[28]

Although the rearrangement of allylic selenoxides to allylic alcohols is, in many respects, analogous to the sulfenate–sulfoxide [2,3] sigmatropic rearrangement there are notable differences.[29] For selenoxides the equilibrium shown in Scheme III overwhelmingly favors the selenenate (ArSe–O–R). The selenoxide and selenenate are rarely detected, rearranging to the allylic alcohol at temperatures as low as −80 °C.[30,31] In a study of the rearrangement of *o*-nitrophenyl prenyl selenoxide to the selenenate Reich and co-workers estimated an exo–endo transition-state energy of 2.0 kcal/mol.[30] More recently, these workers described the [2,3] sigmatropic rearrangement of a diastereomeric selenoxide derived from chiral selenide **16** affording (*S*)-linalool (**17**) in 83% ee via an endo transition state.[12] The minimum chirality transfer for this sequence was estimated to be 83% assuming that the stereoselec-

(23) (a) Pirkle, W. H.; Hoekstra, S. *J. Am. Chem. Soc.* **1976**, *98*, 1832. (b) Pirkle, W. H.; Bare, S. D.; Muntz, R. L. *Tetrahedron Lett.* **1974**, *26*, 2295.

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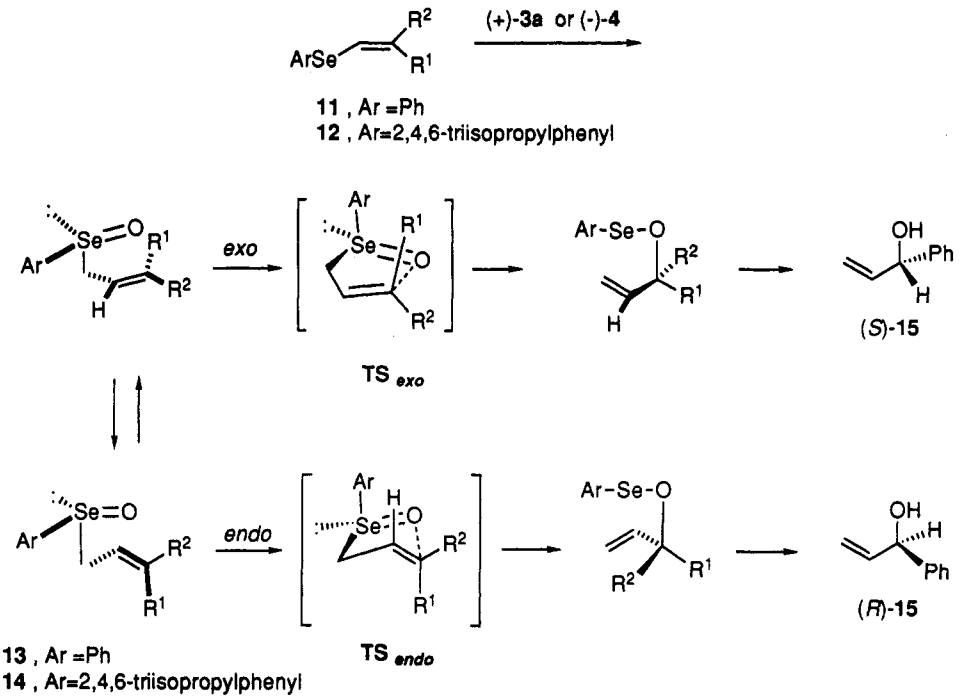
(28) Hoffmann, R. W.; Goldmann, S.; Gerlach, K., Maak, N. *J. Chem. Ber.* **1980**, *113*, 845.

(29) For a review on the allyl selenoxide/allyl selenenate rearrangement see: Reich, H. J. In *Organoselenium Chemistry*; Liotta, D., Ed.; John Wiley & Sons: New York, 1987; Chapter 8.

(30) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154. Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570. Reich, J. J.; Shah, S. K.; Gold, P. M.; Olson, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 3112.

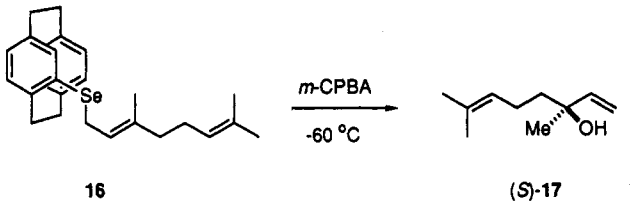
(31) Reich, H. J.; Yelm, E. E.; Wollowitz, S. *J. Am. Chem. Soc.* **1983**, *105*, 2503.

Scheme III[a]



[a] Key: (a) *trans*-R^1 = H, R^2 = Ph; (b) *cis*-R^1 = Ph, R^2 = H.

tivity for the oxidation is similar to the methyl selenide corresponding to **16**.



Our earlier studies of allyl selenoxide–selenenate [2,3] sigmatropic rearrangement using enantiomerically enriched selenoxides also suggested that chirality transfer could be quite high.[2] However, the lack of direct knowledge of the enantiomeric purity of the precursor allylic selenoxide as well as the low ee's (8–12%) made this conclusion tentative.

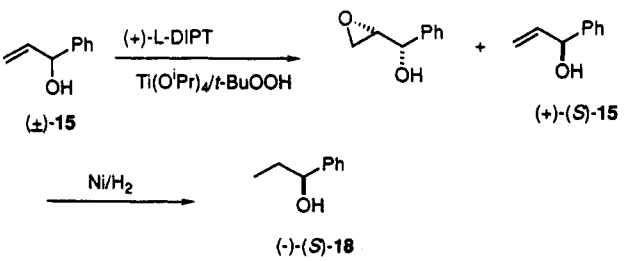
To provide further insights into the stereochemical aspects of the [2,3] sigmatropic rearrangement of allyl selenoxides to allylic selenenates (allylic alcohols) we chose to explore the rearrangement of (*E*)- and (*Z*)-aryl cinnamyl selenoxides **13** and **14** to 1-phenylallyl alcohol (**15**) (Scheme III). The requisite selenides **11** and **12** were prepared in good yield by reaction of the sodium aryl selenolate with (*E*)- and (*Z*)-cinnamyl chloride. The latter chloride (*Z*/*E* (95:5)) was prepared in better than 75% yield simply by treating (*Z*)-cinnamyl alcohol (*Z*/*E* (90:10)) with methanesulfonyl chloride in pyridine. Extensive isomerization is reported to occur on treatment of this alcohol with phosphorus trichloride in pyridine.[32]

Two methods were employed for the asymmetric oxidation of **11** and **12** by 1.5 equiv of (+)-**3** and (−)-**4**. Method A involved addition of water and pyridine to the reaction mixture following oxidation to hydrolyze the selenenate, whereas method B involved addition of pyridine to the selenide prior to oxidation. As previously noted pyridine suppresses readdition of the byproduct benzeneselenenic acid (PhSeOH) to the allylic alcohol.[1] Both **3** and **4** are stable in the presence of pyridine. Oxidation of (*E*)- and (*Z*)-phenyl cinnamyl selenides (**11**) was complete within 5 min at −60 °C whereas the more hindered selenide **12** required oxidation at 0 °C for several hours. 1-Phenylallyl alcohol (**15**) was isolated by chromatography and the enantiomeric purity determined on the Mosher ester prepared by treatment with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride [(*S*)-(+)-MTACl]. Comparison of the chemical shifts of the Mosher ester prepared independently from (*S*)-(+)-**15** was used to de-

Table II. Rearrangement of Allylic Selenoxides 13 and 14 to 1-Phenylallyl Alcohol (15) in $CHCl_3$

entry	selenoxide	oxaziridine	method[a]	allylic alcohol 15 % ee[b] (Config) % Yield[c]	TS
1	(*S*)-(*E*)-**13a**	(+)-**3**[d]	A	4 (*R*) 65	endo
2	(*S*)-(*E*)-**13a**	(−)-**4**	A	35 (*R*) 62	endo
3	(*S*)-(*E*)-**14a**	(+)-**3**[e]	A	25 (*S*) 44	exo
4	(*S*)-(*E*)-**14a**	(+)-**3**	B	31 (*S*) 56	exo
5	(*S*)-(*E*)-**14a**	(−)-**4**	A	36 (*S*) 41	exo
6	(*S*)-(*E*)-**14a**	(−)-**4**	B	40 (*S*) 55	exo
7	(*S*)-(*Z*)-**13b**	(+)-**3**	B	9 (*R*) 35	endo
8	(*S*)-(*Z*)-**13b**	(−)-**4**	B	40 (*R*) 55	endo
9	(*S*)-(*Z*)-**14b**	(+)-**3**	B	42 (*R*) 43	endo
10	(*S*)-(*Z*)-**14b**	(−)-**4**	B	60 (*R*) 46	endo

[a] Method A. After the oxidation was complete the reaction was quenched with water and pyridine. Method B. Pyridine was added prior to oxidation. [b] Determined on the Mosher ester. [c] Isolated yields. [d] Oxidation at −60 °C. [e] Oxidation at 0 °C.



(32) Prochazka, M.; Uchytil, B.; Zelinka, J. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1342.

termined the absolute configuration. Enantiomerically pure (*S*)-(+)-**15** was obtained by Sharpless kinetic resolution of (±)-**15** using (+)-L-diethyl tartrate.[33] The configuration of (*S*)-(+)-**15** was further confirmed by reduction to (*S*)-(−)-phenylethylcarbinol (**18**) related earlier to (*S*)-(+)-mandelic acid by Mosher and co-workers (Table II).[34] The solvent dependency of the optical rotation of **15** makes it unreliable as a measure of absolute configuration or enantiomeric purity.[2]

The results summarized in Table II reveal that modest 1 → 3 chirality transfer occurs in the asymmetric oxidation of allylic selenides **11** and **12**. Interpretation of these results, however, requires several assumptions. The first assumption is that the enantioselective oxidation of **11** and **12** with oxidant (−)-**4** gives selenoxides **13** and **14** >95% ee having the *S* configuration. This assumption is based on the fact that oxidation of **5** gave the (*S*)-selenoxides **6** in >95% ee (Table I). We next assume that selenoxides **13** and **14** are configurationally stable under the reaction conditions transferring all of their chirality to C-3. The configurational stability of **6b–d**, the fact that **13a** and **14a** (Table II, entries 2 and 5) gave similar stereoselectivities, as well as the extremely fast rate of rearrangement of allylic selenoxides to allylic alcohols support this hypothesis. It is also worth noting that the corresponding sulfoxides (*E*)-**13a** (R^1 = H) where R^2 is phenyl or *tert*-butyl, which are configurationally stable, gave racemic allylic alcohols.[28]

Accepting these conditions, then the chirality transfer for the [2,3] sigmatropic rearrangement of allylic selenoxides to allylic alcohols, like allylic sulfoxides, is dictated by the energy difference of the diastereomeric exo and endo transition states (Scheme III). Selenoxide (*E*)-(*S*)-**13a** gives (*R*)-**15** (35% ee) via the endo transition state whereas (*E*)-(*S*)-**14a** gives (*S*)-**15** (36% ee) via the exo transition state (Table II, entries 2 and 5). Allylic strain ($A_{1,3}$) between the bulky 2,4,6-triisopropylphenyl group and C-3 proton in $\mathbf{TS}_{endo}$ favors the exo transition state. The *Z*-allylic selenoxides **13b** and **14b** give (*R*)-**15** via the endo transition state. Here, the unfavorable 1,4-interaction between the Ar and phenyl (R^1) groups favors the endo transition state. This results is consistent with the fact that **14b** (R^1 = 2,4,6-triisopropylphenyl) gives (*R*)-**15** in 60% ee whereas **13b** (R^1 = Ph) gives (*R*)-**15** in 40% ee (Table II, entries 8 and 10).

The modest stereoselectivities observed for the [2,3] sigmatropic rearrangement of allylic selenoxides to allylic alcohols (40–60% ee) support Reich's original estimate of the exo/endo energy of about 2 kcal/mol.[31] However, our results as well as the more recent ones of Reich and Yelm suggest that the extent of chirality transfer is highly dependent on the structure of the allylic selenoxide. Thus, significant improvement in the chirality transfer for this rearrangement is likely by rational modification of the allylic selenide.

Summary

Simple alkyl aryl selenoxides of high enantiomeric purity (90–95% ee) and well-defined stereochemistry are readily available via the asymmetric oxidation of selenides using (+)- or (−)-*N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (**4**). As long as moisture and acid are excluded these selenoxides are configurationally stable. The asymmetric oxidation of *E*- and *Z*-allylic selenides **11** and **12** give optically active 1-phenyl allyl alcohol (**15**) via a concerted [2,3] sigmatropic selenoxide–selenenate rearrangement. The extent of the chirality transfer as well as the endo/exo transition state geometries are highly dependent on the structure of the allylic selenide.

Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points, and elemental analysis have been previously described.[19a] Capillary GLC were performed using a Supelcoport SPB-35 (30-m × 0.75-mm) borosilicate glass column. CD spectra were measured on a JASCO J-414 spectropolarimeter. Glassware, syringes, needles, etc. were oven dried overnight and cooled in a vacuum desiccator. $CDCl_3$ was purchased from Cambridge Isotope Laboratories and dried by distilling over P_2O_5 into a receiver containing anhydrous K_2CO_3. This solvent was preserved over dry 3-Å molecular sieves in an amber bottle covered with aluminium foil and fitted with a rubber septum. Dry methanol was purchased from Aldrich. *trans*-Cinnamyl chloride and diphenyl diselenide were purchased from Aldrich, whereas (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride [(*S*)-(+)-MTACl] was purchased from JPS Chimie (Switzerland). Oxaziridines (+)-**3a**,[35] (−)-**4**,[20] methyl phenyl selenide (**5a**),[2] and bis(2,4,6-triisopropylphenyl) diselenide[7] were prepared by known procedures. Aluminum oxide, activated basic, Brockmann I (150 mesh, 58 Å), was purchased from Aldrich.

General Procedure for the Preparation of Alkyl 2,4,6-Trisopropylphenyl Selenides 5b–d. In a 25-mL three-necked round-bottomed flast equipped with a magnetic stirring bar and septum was placed 0.5 g (0.9 mmol) of bis(2,4,6-trisopropylphenyl) diselenide in 15 mL of methanol followed by addition of 0.6 g (1.8 mmol) of $NaBH_4$ over 15 min. The reaction mixture, which gradually lost the bright orange color of diselenide, was stirred 0.5 h at which time 2 equiv of the appropriate halide was added. After being stirred overnight the reaction mixture was quenched by addition of 5 mL of water and the solvent removed on a rotary evaporator. The residue was extracted with *n*-pentane (20 × 2 mL) and the organic layer washed with water (20 mL) and brine and dried. Removal of the solvent gave the liquid selenide which was purified by distillation.

Methyl 2,4,6-triisopropylphenyl selenide (5b): yield 86%; mp 44–45 °C (lit.[8b] mp 43–44 °C).

Ethyl 2,4,6-trisopropylphenyl selenide (5c): bp_1 90–100 °C; yield 88%; IR (KBr) 1460, 1360, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, 18 H, *J* = 6.9 Hz), 1.24 (s, 3 H), 1.31 (t, 2 H, *J* = 7.46 Hz), 2.64 (q, 2 H, *J* = 7.46 Hz), 2.86 (hept, 1 H, *J* = 7.1 Hz), 3.87 (hept, *J* = 7.1 Hz), 6.98 (s, 2 H); ^{13}C NMR δ 15.5, 23.46, 24.03, 24.63, 34.24, 34.29, 121.46, 126.98, 149.18, 152.97; MS *m/e* 312 (M^+) (^{80}Se). Anal. Calcd for $C_{17}H_{28}Se$: C, 65.38; H, 8.97. Found: C, 64.96; H, 8.45.

***p*-Methoxylbenzyl 2,4,6-triisopropylphenyl selenide (5d)**: $bp_{1.5}$ 180–210 °C; yield 87%; IR (KBr) 1585, 1460, 1380, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, 12 H, *J* = 6.9 Hz), 1.25 (d, 6 H, *J* = 6.9 Hz), 2.9 (hept, 1 H, *J* = 6.9 Hz), 3.76 (s, 3 H), 3.79 (s, 2 H), 3.75–3.86 (m, 2 H), 6.86 (AB quartet, 4 H, *J* = 8.7 Hz), 6.98 (s, 2 H); ^{13}C NMR δ 24.04, 24.57, 33.06, 34.23, 55.2, 113.65, 121.4, 127.42, 129.51, 131.06, 149.51, 153, 158.23; MS *m/e* 404 (M^+) (^{80}Se).

General Procedure for the Asymmetric Oxidation of Selenides 5. In a flame-dried 25-mL two-necked round-bottom flask equipped with a three-way stopcock attached to an argon balloon, a magnetic stirring bar, and a septum was placed 2.0 g of 3-Å molecular sieves. The flask was flushed with argon, 3 mL of dried $CDCl_3$ added, and the solution cooled to −60 or 0 °C prior to addition of 0.5 mmol of the appropriate selenide in 3 mL of $CDCl_3$. To this solution was added dropwise 1.2 equiv of oxaziridines (+)-**3a** or (−)-**4** in 4 mL of $CDCl_3$ via syringe. When the oxidation was complete, as indicated by TLC (5 min for **5a** and 2 h for **5b–d**), the solvent was evaporated to dryness under vacuum (10 mmHg) using the three-way stopcock at 0 °C. The reaction flask was flushed with dry argon, 15 mL of dry *n*-pentane was added via syringe, and the mixture was stirred for 10 min. After the solids had settled, the clear *n*-pentane layer containing the selenoxide was transferred, via syringe, to a second dry round-

(33) Gao, Y.; Hanson, M. R.; Klunder, M. J.; Ko, Y. S.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(34) MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876.

(35) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158.

bottom flask fitted with a three-way stopcock and attached to an argon balloon. Removal of the *n*-pentane solution under vacuum at 0 °C gave the solid selenoxides.

Determination of Enantiomeric Purity. The chemical purity and enantiomeric excess (% ee) were determined on a small portion of the selenoxide using ^{1}H NMR and the chiral shift reagent Eu(hfc)$_3$ for **5a–b**, **5d**, and (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol in the case of **5c**. The selenoxides were dissolved in a minimum amount of dry $CDCl_3$ or C_6D_6 for **5c** and transferred to a dry, argon-flushed NMR tube fitted with a rubber septum and containing 0.5 mL of dry $CDCl_3$ or C_6D_6.

Flash Chromatography of Optically Active Selenoxides. In a flame dried chromatography column was placed 60 g of basic aluminum oxide, activated by heating at 120 °C for 3 h. The selenoxides, dissolved in a minimum amount of dry $CHCl_3$, were loaded on the column under an argon blanket and rapidly eluted (<30 min) using 98:2 dry CH_2Cl_2–MeOH mixture. The samples were collected under argon and the solvent removed on a rotary evaporator flushed with argon to give the selenoxides.

(*S*)-(−)-Methyl 2,4,6-triisopropylphenyl selenoxide (6b): yield 85%; mp 154–154 °C (lit.[8a] mp 154–155 °C); $[\alpha]^{20}_D$ −57° (*c* 1.1, $CHCl_3$) (85% ee); CD (2,2,4-trimethylpentane) 280 ($[\theta]$ −4.04 × 10^4) and 234 ($[\theta]$ + 2.16 × 10^5) nm.

(*R*)-(+)-Methyl 2,4,6-triisopropylphenyl selenoxide (6b): yield 65%; mp 152–153 °C (lit.[8a] mp 154–155 °C); $[\alpha]^{20}_D$ +45.4 (*c* 1.2, $CHCl_3$) (69% ee) CD (2,2,4-trimethylpentane) 280 ($[\theta]$ +2.95 × 10^4) and 234 ($[\theta]$ −5.37 × 10^4) nm.

(*S*)-(−)-Methyl 2,4,6-triisopropylphenyl sulfoxide (9b): yield 95%; mp 112 °C; $[\alpha]^{20}_D$ −182.4° (*c* 2.3, $CHCl_3$) (>95% ee); IR (KBr) 860 (S=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–1.31 (m, 18 H), 2.82–2.86 (m, 1 H), 2.86 (s, 3 H, CH_3), 3.82–3.96 (m, 2 H), 7.1 (s, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.8, 24.16, 24.75, 28.04, 34.32, 40.73, 123.02, 134.06, 135.03, 149.43, 152.12; CD (2,2,4-trimethylpentane) 268 ($[\theta]$ − 5.23 × 10^{10}) and 218 ($[\theta]$ + 8.60 × 10^{10}) nm. Anal. Calcd for $C_{16}H_{26}SO$: C, 72.18; H, 9.77. Found: C, 71.86; H, 9.68.

(*S*)-(−)-Ethyl 2,4,6-triisopropylphenyl selenoxide (6c): yield 60%; mp 86–88 °C dec; $[\alpha]^{20}_D$ −139° (*c* 0.72, $CHCl_3$) (87% ee); IR (KBr) 840 (Se=O) cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.01–1.28 (m, 18 H), 2.9 (hept, 1 H, *J* = 11.3 Hz), 3.75 (s, 3 H), 3.96–4.25 (m, 2 H), 4.36 (q, 2 H, *J* = 11.3 Hz), 7.06 (AB quartet, 4 H, *J* = 8.69 Hz), and 7.18 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.56, 24.19, 24.66, 28.92, 34, 43.7, 122.9, 132.09, 150.95, 151.83; CD (2,2,4-trimethylpentane) 295 ($[\theta]$ − 2.16 × 10^4) and 250 ($[\theta]$ + 7.90 × 10^4); MS *m/e* 420 (M$^+$) (^{80}Se).

(*S*)-(−)-*p*-Methoxybenzyl 2,4,6-triisopropylphenyl selenoxide (6d): yield 68%; mp 112–114 °C; $[\alpha]^{20}_D$ −37.7 (*c* = 0.62, $CHCl_3$) (86% ee); IR (KBr) 845 (Se=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3 H, *J* = 7.7 Hz), 1.1–1.25 (m, 12 H), 1.26 (d, 6 H, *J* = 6.92 Hz), 2.7 (q, 2 H, *J* = 7.7 Hz), 2.85 (hept, 1 H, *J* = 7.1 Hz), 4.15 (hept, 2 H, *J* = 7.1 Hz), 7.1 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.02, 23.63, 28.50, 33.44, 54.47, 55.06, 113.41, 122.22, 127.51, 129.77, 131.18, 150.71, 151.49, 158.61; CD (2,2,4-trimethylpentane) 275 ($[\theta]$ − 1.60 × 10^4) and 225 ($[\theta]$ + 2.34 × 10^4); MS *m/e* 328 (M$^+$) (^{80}Se).

General Procedure for the Preparation of (*E*)- and (*Z*)-Aryl Cinnamyl Selenides 13 and 14. In a 100-mL single-necked flask equipped with a magnetic stirring bar and an argon inlet was placed 4 mmol of the appropriate diaryl diselenide in 30 mL of dry methanol. To the reaction mixture at room temperature over 15 min was added 2.2 equiv of $NaBH_4$, and the reaction mixture was stirred for 0.5 h at which time 2.2 equiv of (*E*)- or (*Z*)-cinnamyl chloride in 10 mL of methanol was added in one portion. After being stirred overnight the solution was quenched by addition of 10 mL of water, the solvent evaporated, and the residue extracted with *n*-pentane (2 × 20 mL). The combined extracts were washed with H_2O and brine (2 × 20 mL) and dried. Removal of the solvent gave an oil which was purified by distillation or crystallization from ethanol.

(*E*)-Phenyl cinnamyl selenide (11a): yield 85%; mp 65–65 °C (lit.[36] mp 64–65 °C); ^{1}H NMR ($CDCl_3$) δ 3.70 (d, 2 H, *J* = 6 Hz), 6.2–6.4 (AB quartet, 2 H, *J* = 15.6 Hz) on irradiation of the allyl signal at δ 3.7, 7.1–7.5 (m, 10 H, Ar).

(*Z*)-Phenyl cinnamyl selenide (11b): yield 90%; bp$_4$ 115–120 °C; IR (neat) 3055, 1676, 1436, 736, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.80 (d, 2 H, *J* = 7.41 Hz), 5.85–5.95 (m, 1 H), 5.87 (d, 1 H, *J* = 11.4 Hz), 7.15–7.53 (m, 10 H).

(*E*)-2,4,6-Triisopropylphenyl cinnamyl selenide (12a): yield 95%; mp 74–76 °C; IR (KBr) 3027, 1643, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 12 H, *J* = 6.9 Hz), 2.26 (d, 6 H, *J* = 6.9 Hz), 2.89 (hept, 1 H, *J* = 6.89 Hz), 3.45 (d, 2 H, *J* = 8.8 Hz), 3.92 (hept, 2 H, 6.89 Hz), 6.08–6.45 (m, 2 H), 7.01 (s, 2 H0, 7.21–7.32 (m, 5 H); MS *m/e* 398 (M$^+$). Anal. Calcd for $C_{24}H_{32}Se$: C, 72.18; H, 8.02. Found: C, 71.70; H, 7.68.

(*Z*)-2,4,6-Triisopropylphenyl cinnamyl selenide (12b): yield 94%; bp$_2$ 130–8 °C; IR (KBr) 3035, 1665, 1457, 740, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 12 H, *J* = 6.94 Hz), 1.26 (d, 6 H, *J* = 6.9 Hz), 2.87 (hept, 1 H, *J* = 6.89 Hz), 3.47 (d, 2 H, *J* = 8.8 Hz), 3.93 (hept, 2 H, *J* = 6.89 Hz), 5.8–5.85 (m, 1 H), 6.43 (d, 1 H, *J* = 11.42 Hz), 6.99 (s, 2 H), 7.04–7.30 (m, 5 H); MS *m/e* 398 (M$^+$). Anal. Calcd for $C_{24}H_{32}Se$: C, 72.18; H, 8.02. Found: C, 71.83; H, 7.65.

Preparation of (*Z*)-Cinnamyl Chloride from (*Z*)-Cinnamyl Alcohol. To a precooled, 0 °C solution of 4.8 g (34.8 mmol) of (*Z*)-cinnamyl alcohol (*Z*:*E* = 90:10) in 30 mL of dry CH_2Cl_2 containing 9.1 mL (3 equiv) of pyridine was added dropwise 4.2 mL (1.6 equiv) of freshly distilled methanesulfonyl chloride. The reaction mixture was stirred at 5 °C and the progress of the reaction monitored by TLC for the absence of the alcohol. After 18 h evaporation of the solvent gave a solid residue which was diluted with 20 mL of water and the solution extracted with *n*-pentane (3 × 50 mL). After the *n*-pentane extracts were washed with H_2O and brine and dried, removal of the solvent under vacuum gave an oil which was purified by flash chromatography (*n*-pentane) to give 4.14 g (75%) of the chloride: *Z*:*E* = 95:5 (by capillary GLC); bp$_6$ 80–90 °C (lit.[37] for the mixture of cis and trans bp$_3$ 85 °C); IR (neat) 3042, 1655, 1485, 1275, 800, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.26 (d, 2 H, *J* = 9.34 Hz), 5.8–5.95 (m, 5 H), 6.64 (s, 1 H, *J* = 11.5 Hz), 7.24–7.34 (m, 5 H).

Preparation of (*Z*)-Cinnamyl Alcohol. This alcohol was prepared by a modification of a reported procedure.[37] In a 500-mL three-necked flask equipped with an argon inlet, stirring bar, a gas inlet tube, and an addition funnel was placed 9.58 g (94 mmol) of phenyl acetylene in 200 mL of ether. Over a period of 45 min was added 61 mL of a 2 M solution of ethylmagnesium bromide (122 mmol 1.3 equiv) in 300 mL of dry diethyl ether and the reaction mixture stirred for 2 h. Formaldehyde gas, generated by heating paraformaldehyde (2 equivalents) at 165 °C, was passed through the reaction mixture via the gas inlet tube with stirring. When the reaction was complete, the solution was poured onto 200 g of crushed ice and neutralized with 20% sulfuric acid. The organic layer was separated and the aqueous layer saturated with NaCl and extracted with ether. The combined organic extracts were washed with brine and dried, and the solvent was removed to give an oil, which was distilled: bp 90–105 °C (lit.[37] bp$_3$ 114–115 °C) to give 9.35 g (77%) of the 3-phenyl-2-propyn-1-ol.

In a Parr hydrogenation apparatus was place 4.8 g (36 mmol) of 3-phenyl-2-propyn-1-ol in 150 mL of dry ethyl acetate, 0.840 g of 5% Lindlar catalyst, and a few drops of quinoline and the apparatus pressurized to 2–5 psi of H_2. The hydrogenation was complete within 15 min, as determined by capillary GLC, at which time the solvent was removed under vacuum and the resulting oil distilled: bp$_5$ 110–114 °C [lit.[37] bp$_5$ 115 °C) to give 4.31 g (95%) of (*Z*)-cinnamyl alcohol. The *Z*/*E* ratio was determined to be 90:10 by GLC.

General Procedure for Asymmetric Oxidation of (*E*)- and (*Z*)-Aryl Cinnamyl Selenide 11 and 12. Method A. In a flame-dried two-necked round-bottom flask equipped with magnetic stirring bar, rubber septum, and a three-way stopcock under an inert atmosphere was placed 0.5 mmol of the appropriate selenide 11 or 12 in 5 mL of dry $CDCl_3$. After the reaction mixture was cooled to −60 °C, 1.2 equiv of oxaziridines 3 or 4 in 4 mL of $CDCl_3$ was added via syringe. After the oxidation was complete, as determined by TLC, 1.0 mL of water containing 0.5 mL of pyridine was added and the solution stirred for 6 h at room

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temperature. The bulk of the solvent was removed on a rotary evaporator and the residue dissolved in 5 mL of CH_2Cl_2, dried, and filtered. The volume was reduced to 1.0 mL and the allylic alcohol isolated by preparative TLC (40% ether–*n*-pentane). The middle TLC band contained 1-phenylallyl alcohol (**15**).

Method B. The procedure described above for method A was followed except that 1 mL of dry pyridine was added prior to oxidation. After the oxidation was complete, stirring was continued for 6 h at which time 1.0 mL of water was added and **15** isolated as described above.

Preparation of Enantiomerically Pure (*S*)-(+)-1-Phenylallyl Alcohol (15) via Kinetic Resolution. The Sharpless epoxidation[33] of 2.68 g (20 mmol) of (±)-1-phenylallyl alcohol (**15**) using (+)-DIPT gave 0.82 g (31%) of (*S*)-(+)-**15** and was isolated by column chromatography eluting with 30% ether–*n*-pentane: bp_6 90–95 °C; $[\alpha]^{20}_D$ +12.34 (neat 0.1-mL cell), $[\alpha]^{20}_D$ −8.4 (*c* 5.0, benzene) (lit.[38] $[\alpha]^{20}_D$ +10.0 (neat, in a 2-mL dm cell).

Hydrogenation of (*S*)-(+)-1-Phenylallylic Alcohol (15) to (−)-(*S*)-Phenylethylcarbinol (18). Hydrogenation of (*S*)-**15** was accomplished as previously reported by Duveen and Kenyon[2,38] to afford (*S*)-(−)-phenylethylcarbinol (**18**): bp_6 110 °C; $[\alpha]^{20}_D$ −21.16 (neat, 0.1-mL cell) [lit.[2] $[\alpha]^{20}_D$ −25.91 (1, 1.0 neat)].

Preparation of the Mosher Ester of (*S*)-(+)-1-Phenylallyl Alcohol (15). In a typical procedure a solution of 33 mg (0.25 mmol) of **15** dissolved in 4 mL of dry CCl_4 was added to 0.2 mL of pyridine, a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and 1.3 equiv of [(*S*)-(+)-MTACl]. The contents were stirred for 4–5 h or until **15** was shown to be absent by TLC. At this time the solution was diluted with 10 mL of CH_2Cl_2, washed with 5% HCl, water, brine, and dried. Removal of the solvent gave a solid which was purified by preparative TLC developing with 80% *n*-pentane–ether to give 85 mg (95%) of the Mosher ester of (*S*)-**15**: IR (neat) 3150, 3040, 1749, 1455, 1248, 1170, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.51 (s, 3 H, OMe), 5.25–5.45 (m, 2 H), 5.9–6.15 (m, 1 H), 6.43–6.56 (m, 1 H), 7.28–7.47 (m, 10 H); MS *m/e* 350 (M^+).

Preparation of the Mosher Ester of (±)-1-Phenylallyl Alcohol (15). The procedure described above was followed to give 87 mg (96%) of alcohol **15**: ^1H NMR ($CDCl_3$) δ 3.41 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 5.25–5.45 (m, 2 H), 5.9–6.15 (m, 1 H), 6.43–6.56 (m, 1 H), 7.28–7.47 (m, 10 H).

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE 9143917).

Registry No. (+)-**3a**, 104322-63-6; (−)-**3a**, 104372-31-8; (−)-**4**, 122270-28-4; **5a**, 4346-64-9; **5b**, 88141-36-0; **5c**, 139706-16-4; **5d**, 139706-17-5; (*S*)-**6a**, 88198-16-7; (*R*)-**6b**, 88198-17-8; (*S*)-**6b**, 88198-18-9; (*S*)-**6c**, 139706-18-6; (*S*)-**6d**, 139706-19-7; (*S*)-**9a**, 5056-07-5; (*S*)-**9b**, 88198-18-9; **11a**, 69562-10-3; **11b**, 105882-08-4; **12a**, 139706-20-0; **12b**, 139706-21-1; (*S*)-(*E*)-**13a**, 139706-23-3; (*S*)-(*Z*)-**13b**, 139706-25-5; (*S*)-(*E*)-**14a**, 139706-24-4; (*S*)-(*Z*)-**14b**, 139706-26-6; (*S*)-**15**, 104713-12-4; (*R*)-**15**, 39623-35-3; (*S*)-**15** (Mosher ester), 139706-22-2; (±)-**15** (Mosher exter), 139706-27-7; (*S*)-(−)-**18**, 613-87-6; (*S*)-(+)-MTACl, 20445-33-4; PhSeSePh, 1666-13-3; (*E*)-cinnamyl chloride, 21087-29-6; (*Z*)-cinnamyl chloride, 39199-93-4; (*Z*)-cinnamyl alcohol, 4510-34-3; phenyl acetylene, 536-74-3; 3-phenyl-2-propyn-1-ol, 1504-58-1; bis-(2,4,6-triisopropylphenyl) diselenide, 71518-96-2.

Supplementary Material Available: ^{13}C NMR spectra of **5d**, **6c**, and **6d** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Synthesis and Characterization of an Insulin-Mimetic Disaccharide

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Received September 10, 1991 (Revised Manuscript Received January 8, 1992)

A glucosaminyl-inositol-1,2-cyclic phosphate, **1**, has been synthesized and evaluated for selected insulin-mimetic properties. The compound was designed to resemble structurally the recently reported inositol glycans which are believed to be insulin second messengers. The synthesis utilized a Koenigs–Knorr glycosylation of optically pure 1-camphanyl-2,3:4,5-di-*O*-cyclohexylidene-D-*myo*-inositol with 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl bromide followed by phosphitylation by the phosphoramidite method, oxidation, and carbodiimide cyclization. Compound **1** was found to stimulate lipogenesis in rat adipocytes in a dose-dependent manner in the micromolar range up to a level 30–40% of that maximally induced by insulin.

Introduction

Diabetes mellitus affects an estimated 15 million people in the United States alone.[1] Of these, 80% are afflicted with non-insulin-dependent diabetes mellitus (NIDDM), a multifactorial disease often characterized by a relative resistance to insulin. These patients are frequently both hyperglycemic and hyperinsulinemic,[2] reflecting both a decreased responsiveness and sensitivity to insulin at the cellular level. Since reductions in insulin binding to target tissue receptors are usually not sufficient to account for the diminished response, it is likely that the biochemical flaw in patients with NIDDM reflects one or more post-receptor defects probably involving transduction of the insulin signal from the target cell surface receptors to the intracellular metabolic machinery. Therefore, an understanding of insulin signal transduction may lead to new strategies for the treatment of NIDDM.

The mechanism by which insulin elicits its anabolic effect on target tissues is still poorly understood. It is generally accepted that the activation of the insulin receptor involves the insulin-dependent stimulation of its protein tyrosine kinase activity resulting in auto-

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0022-3263/92/1957-2606$03.00/0