Stereochemical Studies of Thermal Intermolecular and Intramolecular *N*-Sulfonylimine Ene Reactions

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N-Sulfonylimine **2** has been found to undergo highly stereoselective thermal ene reactions with cyclohexene and *trans*-2-butene. In the cyclohexene example, the exclusive product was unsaturated amino acid derivative **6**, the product of an endo transition state. With *trans*-2-butene, a 9:1 mixture of **18**:**22** was obtained, with the endo product again predominating. Intramolecular ene processes have been effected with the *N*-sulfonylimines derived from glyoxylates **25c** and **26c**. In the former case, the sole ene product was γ-lactone **30** derived from exo addition. In the latter process, a 9:1 mixture of *cis*-(*E*)-lactone **32** and *cis*-(*Z*)-lactone **33** was produced. Lactone **32** results from endo ene transition state **35** and **33** results from endo transition state **36**. All attempts to effect intermolecular ene reactions of *N*-benzoylimine **39** failed. In trying to perform an intramolecular *N*-acylimine ene reaction, only Diels–Alder adduct **45** was produced from precursor **42**.

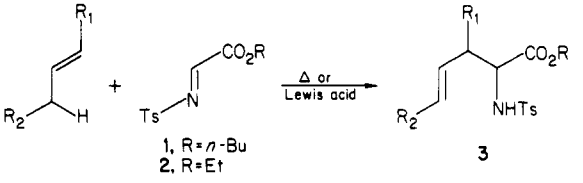
In recent years the ene reaction has finally assumed its rightful place in the synthetic chemist's arsenal of primary carbon–carbon bond-forming methods.[1] Ever increasing numbers of examples of both inter-[1a] and intramolecular[1b] ene processes are now appearing, with particular emphasis toward applications in natural product total synthesis. In addition, the recognition that ene reactions are markedly accelerated by Lewis acids has greatly increased the utility of the methodology.[2]

A variety of multiply bonded ene components containing carbons and/or combinations of heteroatoms have to date been successfully used. However, only recently has the first example of an imine acting as an enophile been reported.[3] Achmatowicz and Pietraszkiewicz discovered that *N*-sulfonylimine **1** reacts with alkenes to afford unsaturated amino acid derivatives **3** (Scheme I). This ene process was found to occur thermally at about 125 °C or to proceed at 0 °C under Lewis acid catalysis to afford good yields of products. It was also reported that with those alkenes where substituent R_2 is alkyl or phenyl, the ene product **3** had the *E* configuration. However, no information was made available about the endo/exo selectivity of the method. Thus, in the situations in which R_1 was a carbon substituent, data were not provided vis-a-vis the diastereomer ratio in **3**, although it did appear in a few cases that sharply melting products were obtained by using olefins capable of producing diastereomeric amino acids derivatives (i.e., cyclohexene, cyclopentene).

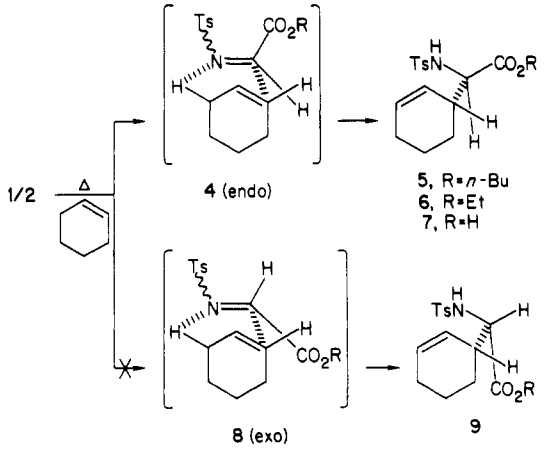
With the hope of ultimately using this reaction in natural product synthesis, we have reinvestigated portions of the published work[3] to establish to what degree this ene process shows endo/exo stereoselectivity.[4] In addition, as discussed below we have found that the *N*-sulfonylimine ene reactions can be effected intramolecularly and have examined the stereochemistry of this type of transformation.

When sulfonylimine **1** and cyclohexene were heated in a sealed tube at 170 °C for 23 h a crystalline adduct **5** was produced (67%) having the melting point reported by Achmatowicz and Pietraszkiewicz.[3] That this material was indeed a *single* compound was evidenced by its ^{13}C NMR

Scheme I



Scheme II



spectrum. In order to work with an ester more readily amenable to NMR analysis, subsequent experiments were performed with sulfonylimine **2**. This compound is easily prepared from commercially available ethyl glyoxylate[6] and *N*-sulfinyl-*p*-toluenesulfonamide[7] as described for formation of **1**.[5] Addition of **2** to cyclohexene again afforded a single ene product **6** in 66% yield. Basic hydrolysis of either the butyl or ethyl ester gave the same crystalline carboxylic acid **7**. The stereochemistry of acid **7** (and thus of **5** and **6**) was firmly established by converting it to iodolactone **10** which showed a coupling constant of 6.1 Hz for H_1/H_2. Snider and co-workers[8] have reported $J = 6.5$ Hz for these protons in the closely related hydroxy-substituted iodolactone **11**. Similarly, the methyl compound **12** was found by Bartlett to have $J_{H_1/H_2} = 6.2$ Hz.[9] The epimeric sulfonamide **13** can be ruled out since iodo-

(1) For reviews see: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Oppolzer, W.; Snieckus, V. *Ibid.* **1978**, *17*, 476.
(2) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
(3) Achmatowicz, O.; Pietraszkiewicz, M. *J. Chem. Soc., Chem. Commun.* **1976**, 484; *J. Chem. Soc., Perkin Trans. 1* **1981**, 2680. See also: Koch, K.; Lin, J. M.; Fowler, F. W. *Tetrahedron Lett.* **1983**, *24*, 1581.
(4) For a preliminary account of a portion of this work see: Tschaen, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 3015; *Ibid.* **1982**, *23*, 4186 (erratum).
(5) Albrecht, R.; Kresze, G. *Chem. Ber.* **1965**, *98*, 1431.
(6) We are grateful to American Hoechst Corporation for a generous gift of ethyl glyoxylate.
(7) Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1456.
(8) Snider, B. B.; van Straten, J. W. *J. Org. Chem.* **1979**, *44*, 3567.
(9) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896.

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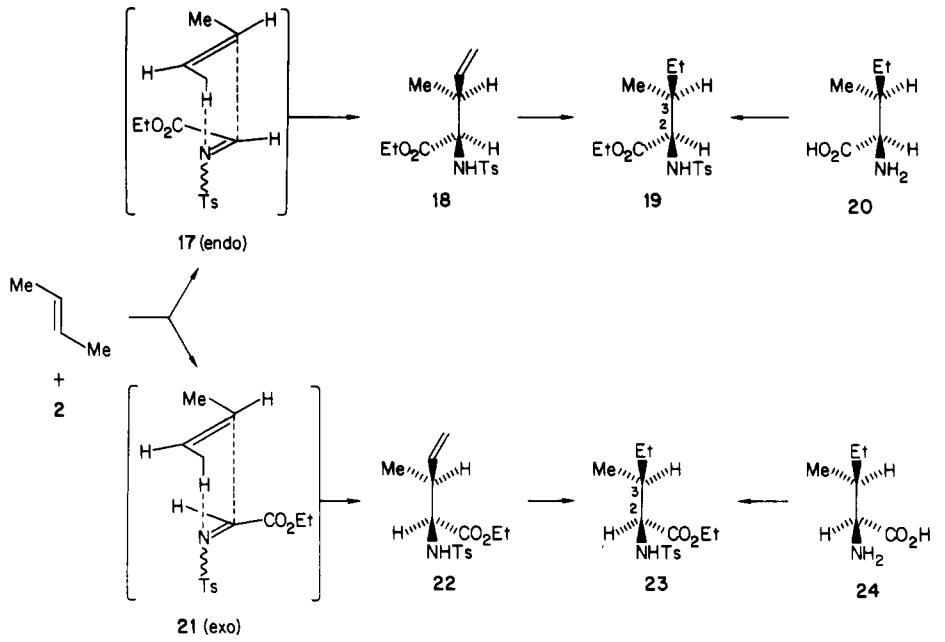
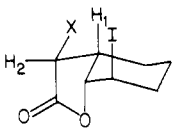
Scheme III

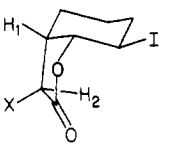


lactones **14** and **15** display J_{H_1/H_2} of 9.6 Hz and 10 Hz, respectively. Also, the very similar lactone **16** has J_{H_1/H_2} = 12.7 Hz.[10]

Therefore, it is clear that adducts **5** and **6** are produced with a high degree of stereoselectivity in the ene reaction. Addition of sulfonylimines **1** and **2** to cyclohexene must proceed via a transition state like **4** (Scheme II) which has the ester carbonyl group endo. Little can be said concerning the reacting configuration of the *N*-sulfonylimine, although it seems reasonable that under the reaction conditions *E*/*Z* isomerization is rapid.[11] Product **9**, which would be derived from the exo transition state **8**, was not detected in the thermal reaction.



10, X=NHTs
11, X=OH
12, X=Me



13, X=NHTs
14, X=OH
15, X=Me
16, X=NHBoc

The closest literature analogy to this result is the thermal ene reaction of methyl glyoxylate with cyclohexene reported by Snider and van Straten to give only a 5% yield of an 8.3:1 mixture of endo/exo products.[8] These workers also found that the yield of ene products could in fact be increased if $FeCl_3$ was used as catalyst, but the endo selectivity decreased to 4.4:1. It should be noted that Whitesell et al.[12] recently reported that reaction of 8-phenylmenthyl glyoxylate with cyclohexene under $SnCl_4$ catalysis afforded a single diastereomeric ene product, but configuration was not determined.

In order to probe the effects of Lewis acids on the *N*-sulfonylimine process a few preliminary experiments were conducted with ferric chloride as catalyst. However, this line of research was not pursued when we observed that mixtures of diastereomers **6** and **9** (R = Et) were being produced.

We have also investigated the thermal reaction of *trans*-2-butene with *N*-sulfonylimine **2**. Upon heating **2** in excess *trans*-2-butene at 150 °C for 20 h an inseparable 9:1 mixture of adducts **18** and **22**, respectively, were formed (77%).[3] The most direct way to determine the stereochemistry of these ene products was to correlate them with commercially available alloisoleucine (**20**) and isoleucine (**24**). Thus, alloisoleucine (**20**) was converted to the ethyl ester and N-tosylated to afford **19** (Scheme III). Similarly, isoleucine (**24**) was transformed to ester sulfonamide **23**. Catalytic hydrogenation of the mixture of ene products **18** and **22** provided an inseparable mixture of **19** and **23**. By comparison of the high-field ^1H NMR of this mixture with that of pure **19** and **23** prepared from the amino acids, it was determined that **18** was the major diastereomer produced in the ene reaction. In particular, the proton at C-2 of **19** is well resolved at δ 3.87, whereas in **23** this proton appears at δ 3.75. The assignments were also corroborated by comparison of the ^{13}C NMR spectra of **19** and **23**.

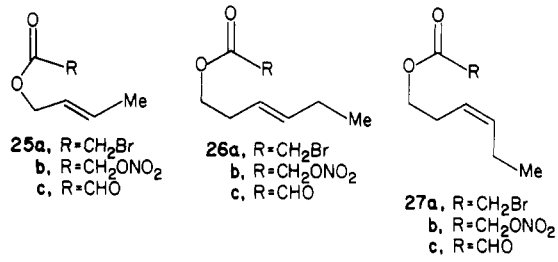
As in the above cyclohexene case, formation of the major isomer **18** involves a transition state **17** having the carbethoxy group endo. The minor product **22** is thus derived from the exo transition state **21**. By comparison, thermal addition of methyl glyoxylate to *trans*-2-butene has been found to give a 20% yield of a 1:0.57 mixture of isomers with the endo product again predominating.[8,12] Clearly imine **2** shows better endo/exo selectivity with both cyclohexene and *trans*-2-butene than does glyoxylate.

An attempt was made to extend this methodology to *cis*-2-butene. On heating this alkene with *N*-sulfonylimine **2** at 150 °C a 79% yield of a 1.5:1 mixture of **18** and **22** was obtained. However, GLC examination of recovered butene indicated it to be a 1:1 mixture of cis and trans isomers. Using triply distilled imine **2** did not change the result, and we are not sure how alkene isomerization is actually occurring. It was therefore not possible to accurately assess the ene endo/exo selectivity with *cis*-2-butene.

We next turned to a study of the feasibility of effecting intramolecular *N*-sulfonylimine ene reactions. For this work we prepared a series of three glyoxylate esters of

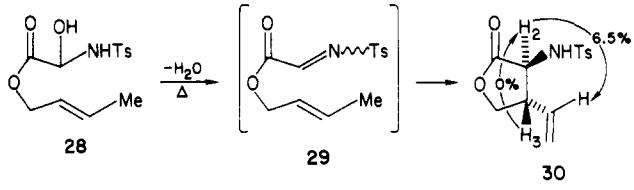
(10) Bartlett, P. A.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 623.
(11) Kalinowski, H. O.; Kessler, H. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Eds.; Wiley-Interscience: New York, 1973; Vol. 7, p 295. McCarty, C. G. In "The Chemistry of the Carbon-Nitrogen Double Bond"; Patai, S., Ed.; Wiley-Interscience: New York, 1970, p 363.
(12) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989.

unsaturated alcohols using the method of Kornblum.[13] Treatment of the bromoacetate **25a**, made from (*E*)-crotyl alcohol, with silver nitrate gave nitrate ester **25b**, which



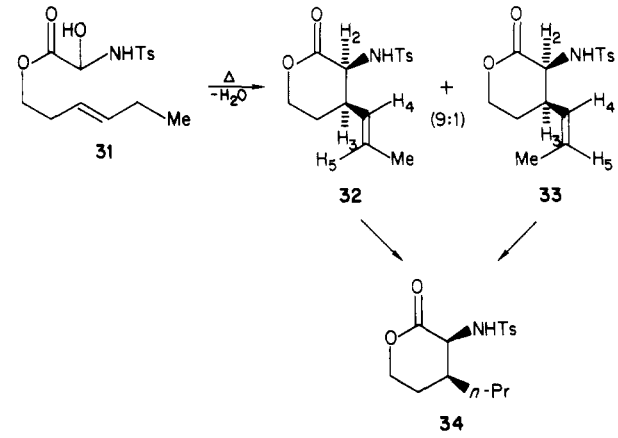
was converted to the known glyoxylate ester **25c**[8] with sodium acetate in Me_2SO. Similarly, bromoacetate **26a** was prepared from (*E*)-3-hexen-1-ol and was transformed to glyoxylate **26a** via nitrate ester **26b**. The corresponding (*Z*)-glyoxylate ester **27c** was also prepared by the same route through intermediates **27a** and **27b**. Not surprisingly, these aldehydes were rapidly hydrated upon exposure to the atmosphere.

Crotyl glyoxylate **25c** was treated with *p*-toluenesulfonamide in benzene containing a catalytic amount of anhydrous aluminum chloride to produce "methylol" derivative **28**.[14] Without purification, **28** was heated in *o*-dichlorobenzene to afford a *single* ene product **30** (35% from **25c**), which undoubtedly arises via *N*-sulfonylimine **29**.



The stereochemistry of butyrolactone **30** was not easily secured by simple ^1H NMR analysis, since the value J_{H_2/H_3} = 9.3 Hz is not unambiguously diagnostic in the absence of the other diastereomer.[8,15] However, the trans structure **30** could be confidently assigned by ^1H nuclear Overhauser enhancement difference spectroscopy (NOEDS) which inter alia showed the enhancements indicated in the drawing.[16] This product is thus the result of an ene transition state having the ester carbonyl group exo. This result is rather puzzling, since it is not clear from inspection of molecular models that the exo transition state is better than the endo. Perhaps this reaction, like the intermolecular ene reaction of dimethyl mesoxylate,[17] involves a late product-like transition state. Oppolzer and Snieckus have pointed out[16] that so-called type I intramolecular ene reactions which form five-membered rings are sometimes reversible processes and products can in principle be formed under either kinetic or thermodynamic control. It is thus not inconceivable that formation of **30** could be due to reversibility of the intramolecular *N*-sulfonylimine ene reaction. However, it is difficult to reconcile the endo stereoselectivity of the reaction of **2** and *trans*-2-butene with this intramolecular example. Interestingly, Snider has found that (*E*)-crotyl glyoxylate **25c** did not undergo either thermal or Lewis acid mediated intramolecular ene reaction and that the corresponding prenyl system gave a low yield of a 1:1 mixture of exo and endo products.[8]

Glyoxylate **26c**, derived from (*E*)-3-hexen-1-ol, was converted to **31** by the procedure used to prepare **28**. Upon heating **31** in refluxing *o*-dichlorobenzene a 9:1 mixture of two δ-lactone ene products were produced which could not be separated chromatographically. However, the major isomer could be purified by crystallization (37%) and has tentatively been assigned stereostructure **32**. This compound clearly has an *E* double bond (J_{vinyl} = 15.1 Hz) but the relative stereochemistry of C-2/C-3 was more difficult to establish. As in the case of γ-lactone **30**, the value J_{H_2/H_3} = 6.8 Hz is not diagnostic for the stereochemistry of **32**.[18]



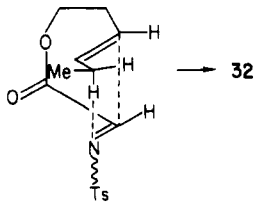
However, based upon NOEDS we believe **32** has the cis C-2/C-3 stereochemistry.[16] Irradiation of H_2 resulted in a large (10.7%) enhancement of H_3. Similarly, irradiation of the olefinic proton H_4 produced only a small (1.6%) enhancement in H_2. Based upon the "normal" infrared carbonyl stretching absorption in **32** (1750 cm^{-1}), this molecule probably exists in a half chair conformation.[19] One cannot reconcile the large H_2/H_3 NOEDS enhancement with the trans stereoisomer which would have a quasi-diaxial relationship of these hydrogens. On the other hand, these results are fully consistent with the cis configuration and a quasi-axial/equatorial disposition of hydrogens H_2/H_3.

The minor adduct **33**, which could be partially purified from the recrystallization mother liquors, has a *Z* disubstituted double bond as evidenced by ^1H NMR (J_{vinyl} = 10.7 Hz). This compound also showed the same H_2/H_3 coupling constant (6.8 Hz) as did the major isomer **32**, therefore indicating cis relative stereochemistry. This stereochemical assignment was supported by the fact that catalytic hydrogenation of both **32** and **33** produced the same saturated lactone **34**.

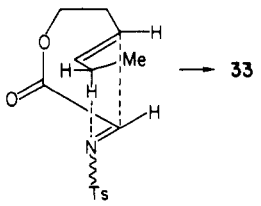
Formation of (*E*)-**32** can be rationalized in terms of an endo ene transition state **35**. Similarly, the minor *Z* product **33** would arise from endo transition state **36**. As in the intermolecular examples of Achmatowicz and Pietraszkiewicz,[3] transition state **35** leading to the *E* double bond is favored since it avoids the $A^{1,3}$ strain[20] between the methyl group and the cis vinyl hydrogen found in transition state **36**.

To our surprise, compound **37**, prepared from glyoxylate **27c**, upon heating afforded the *same* 9:1 mixture of **32** and

(13) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865.
(14) Zaugg, H. E.; Martin, W. B. *Org. React. (N.Y.)* **1965**, *14*, 52.
(15) (a) Tayyeb-Hussain, S. A. M.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480. (b) Altman, J.; Gilboa, H.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 3173.
(16) We are grateful to A. Freyer for measuring these spectra and for his assistance during the course of this work.
(17) Achmatowicz, O.; Szymoniak, J. *J. Org. Chem.* **1980**, *45*, 1228.
(18) For NMR studies of γ-lactones see: Carroll, F. I.; Mitchell, G. N.; Blackwell, J. T.; Sobti, A.; Meck, R. *J. Org. Chem.* **1974**, *39*, 3890 and references cited therein.
(19) Cheung, K. K.; Overton, K. H.; Sim, G. A. *J. Chem. Soc., Chem. Commun.* **1965**, 634.
(20) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.



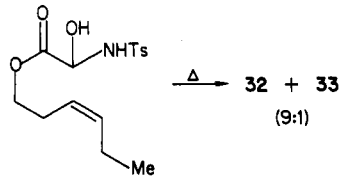
32



33

35 36

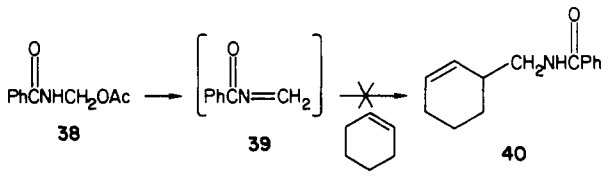
33 as did *E* isomer **31**. Based upon our results with *cis*-2-butene, it seems most likely that the *Z* double bond of **37** may be isomerizing to the *E* before the ene cyclization occurs.



$\xrightarrow{\Delta}$ 32 + 33 (9:1)

37

Since *N*-tosyl protecting groups are often difficult to remove, we decided to explore the possibility of effecting similar ene reactions using *N*-acylimines as the enophile. Methylol acetate **38**[14] was heated with cyclohexene in order to generate ene product **40** via transient *N*-benzoylimine **39**. However, only complex mixtures of products were obtained in these experiments. Similar disappointing results were observed when Lewis acid catalysts were used.[21]



38 39 40

An attempt was also made to perform an *intramolecular* ene reaction of an acylimine. Glyoxylate **25c** was converted to methylol derivative **41** with benzamide.[14] Acetylation of **41** afforded **42**, which upon heating in refluxing *o*-dichlorobenzene did not yield the desired ene product but instead gave dihydrooxazine **45** (64%) as a single stereoisomer. The structure and stereochemistry of this product were proven by analysis of its high-field *E* NMR spectrum. The vicinal coupling constants in this fused system are closely in line with those for monocyclic 5,6-dihydro-4*H*-1,3-oxazines.[15b,22] Thus, the values J_{ab} = 6.0 Hz and J_{bc} = 10.3 Hz are fully consistent with the relative stereochemistry shown in structure **45**.[23]

In addition, the structure and stereochemistry of **45** are in accord with mechanistic reasoning. Formation of this dihydrooxazine undoubtedly involves a [4 + 2] cycloaddition of an acylimine diene and an alkene. Although this type of Diels–Alder reaction is well-known,[24] to our knowledge this is the first example of an intramolecular process. Elimination of acetic acid from acetate **42** can afford an *N*-acylimine having either the *E* (**43A**) or the *Z* (**44A**) configuration.[25] One would anticipate that these two geometric forms should be readily interconvertible under the reaction conditions.[11] From inspection of molecule models, *E* imine **43A** can achieve one reasonably unstrained conformation suitable for the cycloaddition (Scheme IV). This conformer **43B**, having an *exo*-methyl group, would afford the observed product stereoisomer **45**. The *Z*-imine **44A** likewise can achieve one stereoelectronically favorable reacting conformation **44B**, which now has an *endo*-methyl group and is not appreciably strained. This conformation would also produce the observed adduct **45**. Therefore, both *E*- and *Z*-imines should afford the same bicyclic dihydrooxazine **45**, although it is not possible to determine which, if either, route is preferred.

In summary, this work has demonstrated that both inter- and intramolecular ene reactions of *N*-sulfonylimines are highly stereoselective processes with respect to endo/exo products. It does appear that although *N*-acylimines are capable of undergoing a number of cycloaddition reactions,[24,25] they are not useful enophiles. We hope to eventually apply the methodology described here to total synthesis of some natural products.

Experimental Section

Melting points were measured on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 197 spectrophotometer. ^{1}H NMR spectra (60 MHz) were recorded on an EM-360 A NMR spectrometer, and 200-MHz spectra were obtained on a Bruker WP-200 instrument. Coupled, decoupled, and nuclear Overhauser difference ^{1}H spectra (360 MHz) were recorded on a Brüker WM-360 spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian CFT-20 instrument. Mass spectra were recorded at an ionizing voltage of 50–70 eV by electron impact on an Associated Electrical Industries, Ltd. MS-9/50 double-focusing mass spectrometer. Chemical-ionization mass spectra (CIMS) were obtained on a Finnigan 3200 quadrupole mass spectrometer with isobutane as a carrier gas. Analytical and preparative thin-layer chromatography were performed by using E.M. Merck silica gel PF-254. Gravity column chromatography was carried out with 70–230 mesh silica gel 60 (E.M. Merck) as the stationary phase. Flash chromatography was performed on Baker silica gel (25–40 μm).

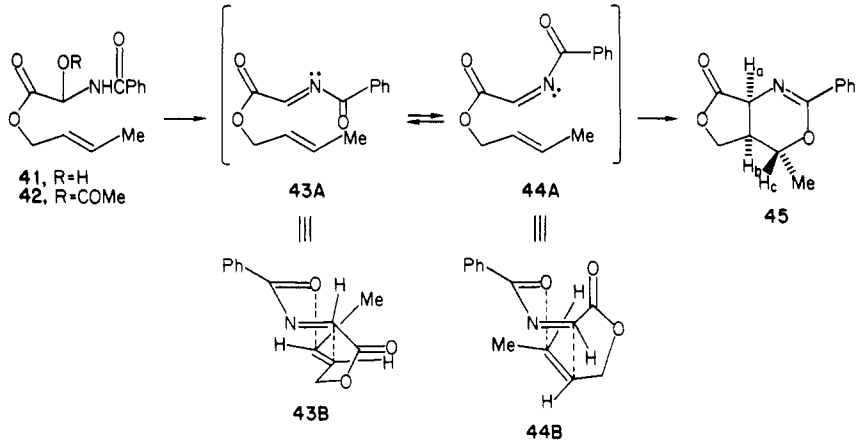
Benzene was distilled from sodium/benzophenone ketyl. Methylene chloride, *o*-dichlorobenzene, dimethyl sulfoxide, and pyridine were distilled from CaH_2. Acetone was dried over anhydrous K_2CO_3 and distilled.

Preparation of *N*-Sulfonylimine 2. A solution of 1.5 g (14.7 mmol) of ethyl glyoxylate (freshly distilled from P_2O_5) and 3.2 g (14.7 mmol) of *N*-sulfinyl-*p*-toluenesulfonamide in 10 mL of dry benzene was heated to reflux. To this mixture was carefully added 0.195 g (1.47 mmol) of anhydrous aluminum chloride in small portions. After 4.5 h the solution was cooled to room temperature and the solvent was removed in vacuo. The residue was distilled in a Kugelrohr apparatus at 145–150 °C (0.02 torr) to yield 2.3 g (63%) of imine **2** as a yellow oil which was redistilled and used immediately: IR (film) 1735, 1630, 1600, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.35 (3 H, t, *J* = 7.0 Hz), 2.50 (3 H, s), 4.40 (2 H, q, *J* = 7.0 Hz), 7.5 (2 H, d, *J* = 8.0 Hz), 7.7 (2 H, d, *J* = 8.0 Hz), 8.28 (1 H, s); CIMS 256 (M^+ + 1).

Ethyl (±)-(*R,*R**)-α-[[(4-Methylphenyl)sulfonyl]-amino]-2-cyclohexene-1-acetate (6).** A solution of 0.150 g (0.59 mmol) of *N*-sulfonylimine **2** in 2 mL of cyclohexene (distilled from $LiAlH_4$) was placed in a heavy-walled glass tube and the solution was saturated with nitrogen for 10 min. The tube was sealed and was heated in an oil bath at 170 °C for 23 h. After the reaction mixture was cooled, excess cyclohexene was removed in vacuo and the crude mixture was chromatographed on two 20 × 20 cm silica gel preparative TLC plates eluting with ethyl acetate–hexane (1:2) to yield 0.131 g (66%) of white crystalline ene product **6**. A sample of **6** was recrystallized from ether–hexane: mp 88–89 °C; IR (KBr) 3250, 1730, 1600, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (3 H, t, *J* = 7.3 Hz), 1.50 (2 H, m), 1.79 (2 H, m), 1.96 (2 H, m), 2.40 (3 H, s), 2.54 (1 H, m), 3.80 (1 H, dd, *J* = 10.4, 4.9 Hz), 3.87 (2 H, q, *J* = 7.3 Hz), 5.08 (1 H, d, *J* = 10.4 Hz), 5.43 (1 H, m),

(21) We thank Dr. N. Khatri for conducting these experiments.
(22) Giordano, C.; Abis, L. *Gazz. Chim. Ital.* **1974**, *104*, 1181. Schmidt, R. R.; Hoffmann, A. R. *Chem. Ber.* **1974**, *107*, 78. Zaugg, H. E. *Synthesis* **1984**, 181.
(23) For a related system see: Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023.
(24) For reviews see: Schmidt, R. R. *Synthesis* **1972**, 333. Kato, T.; Katagiri, N.; Yamamoto, Y. *Heterocycles* **1980**, *14*, 1333.
(25) cf Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573.

Scheme IV



5.85 (1 H, m), 7.27 (2 H, d, J = 7.9 Hz), 7.71 (2 H, d, J = 8.2 Hz); mass spectrum, m/z (relative intensity) 337 (1), 264 (13), 256 (58), 155 (96), 91 (86); exact mass calcd for $C_{17}H_{23}NO_4S$ 337.1348, found 337.1349. Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.50; H, 6.88. Found: C, 60.44; H, 6.94.

n-Butyl ester **5** was prepared in 67% yield by the reported procedure from imine **1** and cyclohexene.[3] A sample was recrystallized from hexane: mp 61–62 °C (lit.[3] mp 61 °C); IR (film) 3300, 1730, 1600, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.88 (3 H, t, J = 7.3 Hz), 1.24 (2 H, m), 1.42 (2 H, m), 1.51 (2 H, m), 1.75 (2 H, m), 1.96 (2 H, m), 2.41 (3 H, s), 2.54 (1 H, m), 3.80 (1 H, dd, J = 10.4, 6.4 Hz), 3.82 (2 H, t, J = 6.7 Hz), 5.13 (1 H, m), 5.43 (1 H, d, J = 10.4 Hz), 5.85 (1 H, m), 7.27 (2 H, d, J = 8.2 Hz), 7.71 (2 H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.18, 143.37, 136.14, 131.66, 129.44, 127.26, 124.44, 66.21, 59.45, 43.85, 30.26, 25.71, 24.70, 21.41, 21.23, 18.87, 13.47; mass spectrum, m/z (relative intensity) 365 (1), 284 (86), 155 (100), 91 (99); exact mass calcd for $C_{19}H_{27}NO_4S$ 365.1661, found 365.1660.

(±)-(*R,*R**)-α-[[(4-Methylphenyl)sulfonyl]amino]-2-cyclohexeneacetic Acid (7).** To a solution of 0.109 g (2 mmol) of potassium hydroxide in 10 mL of water was added 0.074 g (0.2 mmol) of *n*-butyl ester **5** in 10 mL of ethanol. The mixture was heated at 50 °C for 20 h. After the mixture was cooled to room temperature, ethanol was removed in vacuo and the residue was acidified with concentrated HCl. The mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic extracts were dried ($MgSO_4$). The solvent was removed in vacuo affording 0.062 g (100%) of white crystalline acid **7**. A sample of **7** was recrystallized from ethanol–hexane: mp 180–181 °C; IR (film) 3200, 1700, 1600, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.48 (2 H, m), 1.73 (2 H, m), 1.95 (2 H, m), 2.40 (3 H, s), 2.55 (1 H, m), 3.78 (1 H, dd, J = 9.8, 6.1 Hz), 5.54 (2 H, m), 5.75 (1 H, m), 6.51 (1 H, d, J = 9.8 Hz), 7.35 (2 H, d, J = 7.9 Hz), 7.73 (2 H, d, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.19, 143.87, 139.34, 130.88, 130.24, 127.98, 126.71, 60.54, 39.46, 26.70, 25.50, 22.16, 21.39; mass spectrum, m/z (relative intensity) 309 (1), 228 (40), 91 (98), 81 (100); exact mass calcd for $C_{15}H_{19}NO_4S$ 309.1035, found 309.1015. Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19. Found: C, 57.87; H, 6.44.

(±)-(3α,3aβ,7β,7a)-4-Methyl-*N*-(octahydro-7-iodo-2-oxo-3-benzofuranyl)benzenesulfonamide (10). To a solution of 0.022 g (0.07 mmol) of acid **7** in 5 mL of water was added 0.012 g (0.14 mmol) of sodium bicarbonate. The mixture was dissolved by gentle heating and was cooled to 0 °C in an ice bath. To this mixture was added a solution of 0.015 g (0.09 mmol) of potassium iodide and 0.011 g (0.09 mmol) of iodine in 3 mL of water. After 1 h at 0 °C the mixture was warmed to room temperature, was stirred for an additional 20 h, and was extracted with ether. The organic extract was washed with sodium bisulfite, brine, and water, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with ethyl acetate–hexane (1:2) to provide 0.018 g (60%) of the white crystalline iodolactone **10**: mp 101–102 °C; IR (KBr) 3250, 1790, 1600, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (4 H, m), 1.94 (2 H, m), 2.45 (3 H, s), 3.16 (1 H, m), 3.97 (1 H, dd, J = 6.1, 3.7 Hz), 4.65 (1 H, m), 4.76 (1 H, m), 5.10 (1 H, d, J = 3.7 Hz), 7.35 (2 H, d, J = 8.2 Hz), 7.35 (2 H, d, J = 8.2 Hz); mass spectrum, m/z (relative intensity) 435 (0.3), 308 (5), 155 (60), 91 (100); exact mass calcd for $C_{15}H_{18}NO_4SI$ 435.0003, found 435.0015. Anal. Calcd for $C_{15}H_{18}NO_4SI$: C, 41.39; H, 4.17. Found: C, 41.49; H, 4.46.

Ene Reaction of *N*-Sulfonylimine 2 with *trans*-2-Butene. *trans*-2-Butene (2 mL) was distilled from CaH_2 into a heavy-walled glass tube, and 0.125 g (0.49 mmol) of *N*-sulfonylimine **2** in 2 mL of benzene was added. Nitrogen was passed through the mixture for 10 min. The tube was sealed and was heated in an oil bath at 150 °C for 20 h. After the mixture was cooled, the solvent and excess butene were removed in vacuo and the residue was chromatographed on two 20 × 20 cm silica gel preparative TLC plates with ethyl acetate–hexane (1:1) as eluant to provide 0.117 g (77%) of an inseparable 9:1 mixture of **18** and **22**: IR (film) 3300, 2950, 1735, 1600, 1340, 1160, 805 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.04 (3 H, d, J = 6.7 Hz), 1.06 (3 H, t, J = 7.0 Hz), 2.40 (3 H, s), 2.52 (0.9 H, m, major isomer), 2.67 (0.1 H, m, minor isomer), 3.84 (1 H, m), 3.91 (2 H, q, J = 7.0 Hz), 5.01 (2 H, m), 5.30 (0.1 H, d, J = 9.5 Hz, NH, minor isomer), 5.40 (0.9 H, d, J = 10.0 Hz, NH, major isomer), 5.62 (1 H, m), 7.27 (2 H, d, J = 5.5 Hz), 7.71 (2 H, d, J = 8.2 Hz); mass spectrum, m/z (relative intensity) 311 (3), 256 (65), 238 (13), 155 (100), 91 (78), 65 (12).

D-*N*-(*p*-Tolylsulfonyl)alloisoleucine Ethyl Ester (19). Hydrogen chloride gas was bubbled through 6 mL of absolute ethanol for 5 min. To this solution was added 0.100 g (0.76 mmol) of D-alloisoleucine (**20**, Pfaltz and Bauer) and the mixture was heated at reflux for 3.5 h. After the mixture was cooled, the solvent was removed in vacuo to provide 0.121 g (100%) of the ethyl ester as a colorless oil, which was used in the next step without purification.

A solution of 0.121 g (0.76 mmol) of the above ester in 5 mL of methylene chloride was cooled to 0 °C in an ice bath, and triethyl amine (0.5 mL) was added. To this was added 0.145 g (0.76 mmol) of *p*-toluenesulfonyl chloride and the mixture was stirred at 0 °C for 1 h and at room temperature for an additional 45 h. The reaction mixture was washed with water and extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated to dryness in vacuo. Chromatography of the crude product on two 20 × 20 cm silica gel preparative TLC plates eluting with ethyl acetate–hexane (1:2) afforded 0.195 g (82%) of **19** as a white solid. A sample of **19** was recrystallized from ethyl acetate–hexane: mp 82–83 °C; IR (film) 3280, 1730, 1600, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.82 (3 H, d, J = 6.7 Hz), 0.91 (3 H, t, J = 7.3 Hz), 1.06 (3 H, t, J = 7.0 Hz), 1.35 (2 H, m), 1.77 (1 H, m), 2.40 (1 H, m), 2.40 (3 H, s), 3.87 (1 H, dd, J = 6.6, 3.7 Hz), 3.88 (2 H, q, J = 7.0 Hz), 5.30 (1 H, d, J = 9.8 Hz), 7.28 (2 H, d, J = 8.5 Hz), 7.72 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 171.49, 143.46, 136.84, 129.48, 127.35, 61.37, 59.12, 38.14, 25.93, 21.93, 14.21, 13.89, 11.46; mass spectrum, m/z (relative intensity) 313 (0.4), 256 (4), 240 (100), 155 (52), 91 (62); exact mass calcd for $C_{15}H_{23}NO_4S$ 313.1348, found 313.1321. Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.47; H, 7.41. Found: C, 57.43; H, 7.57.

L-*N*-(*p*-Tolylsulfonyl)isoleucine Ethyl Ester (23). This compound was prepared from L-isoleucine (**24**, Sigma) in 84% yield as described above for **19**. A sample was recrystallized from

ethyl acetate–hexane: mp 51 °C; IR (film) 3280, 1730, 1600, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.87 (3 H, t, J = 7.3 Hz), 0.91 (3 H, d, J = 7.0 Hz), 1.07 (3 H, t, J = 7.0 Hz), 1.19 (2 H, m), 1.41 (1 H, m), 2.41 (3 H, s), 3.75 (1 H, dd, J = 9.8, 5.1 Hz), 3.88 (2 H, q, J = 7.0 Hz), 5.16 (1 H, d, J = 9.8 Hz), 7.28 (2 H, d, J = 8.5 Hz), 7.72 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 171.19, 143.44, 136.75, 129.48, 127.29, 61.27, 60.20, 38.47, 24.63, 21.43, 15.32, 13.77, 11.23; mass spectrum, m/z (relative intensity) 313 (0.1), 240 (100), 91 (99); exact mass calcd for $C_{15}H_{23}NO_4S$ 313.1348, found 313.1327. Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.47; H, 7.41. Found: C, 57.48; H, 7.69.

Hydrogenation of the Mixture of Ene Products 18 and 22. To a solution of 0.050 g (0.16 mmol) of the 9:1 mixture of alkenes **18** and **22** in 8 mL of absolute methanol was added 0.010 g of 10% Pd/C. The mixture was stirred at room temperature under 1 atm of hydrogen for 12 h and was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with ethyl acetate–hexane (1:2) to provide 0.045 g (90%) of an inseparable 9:1 mixture of hydrogenation products **19** and **23**, identified by comparison of its ^1H NMR spectrum with those of authentic compounds prepared above.

(*E*)-3-Hexenyl Bromoacetate (26a). A solution of (*E*)-3-hexen-1-ol (1.32 g, 13.2 mmol) and pyridine (2.0 mL) in 10 mL of methylene chloride was cooled to 0 °C. A solution of bromoacetyl bromide (3.48 g, 17.2 mmol) in 15 mL of methylene chloride was added dropwise with stirring over a period of 10 min. The mixture was stirred for 20 min, poured onto 100 mL of ice, and extracted five times with 50 mL of methylene chloride. The organic extract was washed with 100 mL of 5% HCl solution and 100 mL of water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residual oil was distilled (64 °C, 0.3 torr) to yield 2.49 g (85%) of colorless **26a**: IR (film) 2970, 1740, 1285, 1165, 1110, 1000, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.45 (2 H, m), 4.13 (2 H, t, J = 6.5 Hz), 3.80 (2 H, s), 2.60–1.80 (4 H, m), 0.96 (3 H, t, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 123 (12), 121 (12), 82 (100), 67 (87), 55 (15), 41 (39), 39 (17), 28 (16).

Esters **25a** and **27a** were prepared in a similar manner from the corresponding alcohols:

(*Z*)-3-Hexenyl bromoacetate (27a): 100% (colorless oil); bp 69 °C (0.4 torr); IR (film) 2970, 1740, 1285, 1165, 1110, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.30 (2 H, m), 4.07 (2 H, t, J = 6.5 Hz), 3.76 (2 H, s), 2.60–1.80 (4 H, m), 0.96 (3 H, t, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 123 (12), 121 (12), 82 (100), 67 (67), 41 (23), 28 (27).

(*E*)-2-Butenyl bromoacetate (25a): 81% (colorless oil); bp 64 °C (1.2 torr); IR (film) 2970, 1740, 1675, 1280, 1160, 1105, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.70 (2 H, m), 4.53 (2 H, d, J = 5.2 Hz), 3.85 (2 H, s), 1.72 (3 H, d, J = 5.6 Hz); mass spectrum, m/z (relative intensity) 195 (1), 193 (1), 124 (25), 122 (26), 114 (100), 72 (96), 39 (47), 28 (81).

Synthesis of Nitrate Ester 26b. Silver nitrate (5.70 g, 33.6 mmol) was added to a stirred solution of bromo ester **26a** (3.70 g, 16.7 mmol) in 10 mL of acetonitrile. The mixture was stirred in the dark for 24 h and was evaporated in vacuo. The residue was taken up in 20 mL of diethyl ether and filtered. The filter cake was washed with 250 mL of diethyl ether. The combined filtrate was washed with 100 mL of water and was dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo yielded 3.20 g (94%) of **26b** as a colorless oil, which was judged by TLC and ^1H NMR to be sufficiently pure for use in the next step: bp 90 °C (0.7 torr); IR (film) 2980, 1765, 1660, 1295, 1210, 1060, 1000, 970, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.37 (2 H, m), 4.85 (2 H, s), 4.13 (2 H, t, J = 6.6 Hz), 2.60–1.80 (4 H, m), 0.95 (3 H, t, J = 7.3 Hz); mass spectrum, m/z (relative intensity) 82 (100), 67 (73), 55 (31), 41 (37), 28 (74).

Esters **25b** and **27b** were prepared by the above procedure:

Nitrate ester 27b: 92% (colorless oil); bp 78 °C (0.5 torr); IR (film) 2975, 1765, 1660, 1295, 1210, 1060, 1000, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.37 (2 H, m), 4.87 (2 H, s), 4.15 (2 H, t, J = 6.8 Hz), 2.60–1.80 (4 H, m), 0.95 (3 H, t, J = 7.3 Hz); mass spectrum, m/z (relative intensity) 82 (100), 67 (76), 55 (35), 41 (41), 28 (20).

Nitrate ester 25b: 96% (colorless oil); bp 55 °C (0.3 torr); IR (film) 2960, 1760, 1655, 1290, 1205, 1055, 995, 965, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.67 (2 H, m), 4.88 (2 H, s), 4.57 (2 H, d, J = 5.2 Hz), 1.70 (3 H, d, J = 5.2 Hz); mass spectrum, m/z (relative intensity) 175 (1), 71 (59), 55 (100), 41 (39), 39 (17), 28 (16).

Preparation of Glyoxylate 26c. Anhydrous sodium acetate (0.335 g, 4.08 mmol) was added to a stirred solution of **26b** (0.812 g, 4.00 mmol) in 10 mL of dimethyl sulfoxide. After stirring for 20 min, the mixture was poured into 50 mL of ice/brine and was extracted five times with 30 mL of diethyl ether. The ether extract was washed with 50 mL of saturated sodium bicarbonate solution and with 50 mL of water. The aqueous phases were back extracted three times with 50 mL of diethyl ether. The ether layers were combined, dried over anhydrous magnesium sulfate, and evaporated to yield 0.539 g of a viscous yellow oil. Kugelrohr distillation of this material in vacuo from phosphorous pentoxide gave 0.447 g (72%) of colorless **26c**, which hydrated rapidly upon exposure to the atmosphere: bp 90–95 °C (0.4 torr); IR (film) 3450 (br), 2975, 1745, 1460, 1225 (br), 1100 (br), 970 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 9.33 (0.2 H, s), 5.37 (3 H, m), 4.83 (1.4 H, br), 4.20 (2 H, t, J = 6.6 Hz), 2.60–1.80 (4 H, m), 0.96 (3 H, t, J = 7.3 Hz).

Aldehydes **25c** and **27c** were prepared by the above procedure:

Glyoxylate 27c: 85% (colorless oil); bp 90–95 °C (0.4 torr); IR (film) 3450 (br), 2960, 1750, 1460, 1100 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 9.34 (0.2 H, s), 5.34 (3 H, m), 4.81 (1.4 H, br), 4.15 (2 H, t, J = 7.0 Hz), 2.60–1.80 (4 H, m), 0.93 (3 H, t, J = 7.3 Hz).

Glyoxylate 25c: 73% (colorless oil)[8]; bp 85–90 °C (0.4 torr); IR (film) 3450 (br), 2950, 2740, 1740, 1675, 1445, 1210 (br), 1100 (br), 965 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 9.40 (0.3 H, s), 5.88 (2.5 H, m), 5.33 (0.7 H, br m), 4.67 (2 H, m), 1.70 (3 H, d, J = 5.2 Hz).

Synthesis of δ-Lactones 32 and 33. *p*-Toluenesulfonamide (0.520 g, 3.04 mmol) and a catalytic amount of anhydrous aluminum chloride were added to a solution of glyoxylate **26c** (0.447 g, 2.86 mmol) in 15 mL of benzene, and the mixture was refluxed for 24 h. The solvent was removed in vacuo, and 10 mL of ethyl acetate was added to dissolve the residue. The solution was washed with 50 mL of water, and the aqueous layer was back extracted three times with 50 mL of ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 0.892 g of a white solid, which was not purified prior to the next step.

o-Dichlorobenzene (10 mL) was added to 0.132 g of the above solid, and the mixture was refluxed for 7 h. Removal of the solvent in vacuo gave a yellow oil/solid, which was purified by preparative TLC eluting with 1:1 ethyl acetate–hexane to afford 0.048 g (37% from **26c**) of white crystalline **32**: mp 153 °C (recrystallized from ethyl acetate–hexane); IR (film) 3280 (br), 2930, 1750, 1600, 1340, 1165, 970, 815, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.75 (2 H, d, J = 8.3 Hz), 7.28 (2 H, d, J = 8.2 Hz), 5.48 (1 H, dd, J = 15.1, 6.5 Hz), 5.35 (1 H, d, J = 7.0 Hz), 5.09 (1 H, ddd, J = 15.1, 9.3, 1.4 Hz), 4.30 (2 H, m), 4.17 (1 H, t, J = 6.8 Hz), 3.06 (1 H, dd, J = 9.3, 6.8 Hz), 2.40 (3 H, s), 2.25 (1 H, m), 1.86 (1 H, m), 1.64 (3 H, dd, J = 6.5, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 170.43, 143.62, 137.02, 131.15, 129.58, 127.32, 126.99, 65.79, 54.31, 39.31, 28.07, 21.40, 17.84; mass spectrum, m/z (relative intensity) 309 (2), 155 (15), 154 (27), 91 (27), 82 (26), 81 (100), 67 (15), 49 (14), 28 (13); exact mass calcd for $C_{15}H_{19}NO_4S$ 309.1035, found 309.1028.

Concentration in vacuo of the recrystallization mother liquors of **32** gave a white solid, which by ^1H NMR ($CDCl_3$, 360 MHz) was a 1:1 mixture of adducts **32** and **33**. Those signals that could be assigned to protons of minor isomer **33** appeared at δ 5.74 (1 H, ddd, J = 10.7, 6.9, 0.9 Hz) which was olefinic proton H_5, and at δ 3.56 (1 H, m), which was allylic proton H_3.

A similar procedure was used for synthesis of butyrolactone **30**: 35% from **25c** (white crystals): mp 135 °C (recrystallized from ethyl acetate); IR (film) 3280 (br), 2930, 1790, 1640, 1600, 1340, 1160, 820, 670 cm^{-1}; ^1H NMR (acetone-d_6, 360 MHz) δ 7.81 (2 H, d, J = 8.3 Hz), 7.39 (2 H, d, J = 8.2 Hz), 6.94 (1 H, d, J = 8.3 Hz), 5.73 (1 H, ddd, J = 17.2, 10.4, 8.6 Hz), 5.13 (1 H, dd, J = 10.4, 0.9 Hz), 4.96 (1 H, dt, J = 17.1, 1.2 Hz), 4.64 (1 H, t, J = 8.1 Hz), 4.50 (1 H, dd, J = 9.2, 5.2 Hz), 4.20 (1 H, dd, J = 9.3, 0.6 Hz), 3.27 (1 H, m), 2.42 (3 H, s); ^{13}C NMR (acetone-d_6) δ 173.05, 143.50, 139.01, 132.96, 129.73, 127.32, 118.89, 69.90, 55.32, 43.95, 20.76; mass spectrum, m/z (relative intensity) 281 (8), 236 (13), 155 (31), 126 (100), 92 (15), 91 (93), 82 (12), 80 (13), 65 (13), 54

(92), 28 (15); exact mass calcd for $C_{13}H_{15}NO_4S$ 281.0722, found 281.0732.

Hydrogenation of Ene Product 32. To a solution of 0.036 g (0.12 mmol) of alkene **32** in 10 mL of ethyl acetate was added 0.010 g of 10% Pd/C. The mixture was stirred under 1 atm of hydrogen for 12 h, was filtered through Celite, and was concentrated in vacuo to provide 0.036 g (100%) of white crystalline **34**: mp 154 °C (recrystallized from ethyl acetate–hexane); IR (film) 3275, 2960, 1740, 1350, 1170, 815, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.76 (2 H, d, J = 8.3 Hz), 7.31 (2 H, d, J = 8.5 Hz), 5.55 (1 H, d, J = 5.0 Hz), 4.33 (1 H, m), 4.24 (1 H, m), 4.05 (1 H, dd, J = 6.8, 5.0 Hz), 2.47 (1 H, m), 2.42 (3 H, s), 2.11 (1 H, m), 1.80 (1 H, m), 1.66 (1 H, m), 1.36 (1 H, m), 1.12 (1 H, m), 0.92 (1 H, m), 0.87 (3 H, t, J = 7.3 Hz); mass spectrum, m/z (relative intensity) 239 (26), 210 (78), 156 (70), 155 (48), 91 (100), 84 (22), 65 (29), 55 (28), 41 (25), 28 (46).

Preparation of Diels–Alder Adduct 45. Benzamide (0.500 g, 4.13 mmol) was added to a stirred solution of glyoxylate **25c** (0.481 g, 3.75 mmol) in 15 mL of dry acetone. The solution was stirred at room temperature for 62 h. Removal of the solvent in vacuo gave a solid which was purified by preparative TLC (ethyl acetate–hexane, 1:1) to afford 0.535 g (57%) of white crystalline methylol **41**: mp 99.5–100 °C (recrystallized from ethyl acetate–hexane; IR (film) 3310 (br), 2945, 1750, 1645, 1535, 1210, 1090, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.82 (2 H, m), 7.50 (3 H, m), 5.80 (3 H, m), 4.65 (2 H, d, J = 5.2 Hz), 4.60 (2 H, br), 1.70 (3 H, d, J = 6.6 Hz).

Methylol **41** (0.166 g, 0.666 mmol) was dissolved in 10 mL of methylene chloride, and pyridine (0.55 mL, 6.80 mmol) and acetic anhydride (0.65 mL, 6.88 mmol) were added dropwise with stirring. A catalytic amount of 4-(dimethylamino)pyridine was added, and the mixture was stirred at room temperature for 5 min. The mixture was poured into 30 mL of water and extracted four times with 25 mL of methylene chloride. The organic layer was washed successively with 20 mL of 5% HCl solution, 20 mL of saturated $NaHCO_3$ solution, and 20 mL of water and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo yielded 0.193 g (100%) of acetate **42** as a colorless oil, which was judged by TLC and ^1H NMR to be sufficiently pure for use in the next step: IR (film) 3350 (br), 2930, 1750, 1675, 1525, 1235, 1030, 970, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.90–7.20 (5 H, m), 6.59 (1 H, d, J = 9.0 Hz), 5.70 (2 H, m), 4.62 (2 H, d, J = 5.2 Hz), 2.12 (3 H, s), 1.68 (3 H, d, J = 4.6 Hz); mass spectrum, m/z (relative intensity) 231 (9), 192 (14), 150 (31), 105 (100), 77 (24), 43 (16).

Acetate **42** (0.057 g, 0.20 mmol) was dissolved in 5 mL of *o*-dichlorobenzene, and the solution was refluxed for 20 h. The solvent was removed in vacuo, and the residue was purified by preparative TLC (ethyl acetate–hexane, 1:1) to yield 0.029 g (64%) of dihydrooxazine **45** as a colorless oil: IR (film) 2980, 1785, 1650, 1320, 1285, 1175, 1130, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.03 (2 H, d, J = 8.3 Hz), 7.43 (3 H, m), 4.54 (1 H, d, J = 7.5 Hz), 4.51 (1 H, dd, J = 10.1, 6.1 Hz), 4.22 (1 H, dd, J = 10.1, 1.5 Hz), 3.98 (1 H, dq, J = 10.3, 6.2 Hz), 2.53 (1 H, dddd, J = 10.3, 7.5, 6.1, 1.5 Hz), 1.54 (3 H, d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 173.67, 157.50, 132.57, 131.16, 127.99, 127.65, 69.13, 66.43, 54.60, 37.68, 18.96; mass spectrum, m/z (relative intensity) 231 (28), 105 (100), 77 (24), 28 (12); exact mass calcd for $C_{13}H_{13}NO_3$ 231.0911, found 231.0903.

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Registry No. **1**, 2292-87-7; **2**, 83670-53-5; (±)-**5**, 93455-11-9; (±)-**6**, 93455-12-0; (±)-**7**, 93455-13-1; (±)-**7**·Na, 93455-14-2; (±)-**10**, 93455-15-3; (±)-**18**, 93455-16-4; (±)-**19**, 83670-59-1; **20**, 1509-35-9; **20** ethyl ester, 3082-86-8; (±)-**22**, 93455-17-5; (±)-**23**, 93455-18-6; **24**, 73-32-5; **24** ethyl ester, 921-74-4; **25a**, 93455-19-7; **25b**, 93455-20-0; **25c**, 93455-21-1; **26a**, 90449-00-6; **26b**, 93455-22-2; **26c**, 93455-23-3; **27a**, 93455-24-4; **27b**, 93455-25-5; **27c**, 93455-26-6; **28**, 93455-27-7; **29**, 93455-28-8; (±)-**30**, 93455-29-9; **31**, 93455-30-2; (±)-**32**, 93455-31-3; (±)-**33**, 93455-32-4; (±)-**34**, 93455-33-5; **37**, 93455-34-6; **38**, 28482-69-1; **39**, 81793-17-1; **40**, 93455-35-7; **41**, 93455-36-8; **42**, 93455-37-9; (±)-**45**, 93455-38-0; ethyl glyoxylate, 924-44-7; cyclohexene, 110-83-8; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1; *N*-sulfinyl-*p*-toluenesulfonamide, 4104-47-6; benzamide, 55-21-0; (*E*)-3-hexen-1-ol, 928-97-2; (*E*)-2-buten-1-ol, 504-61-0; (*Z*)-3-hexen-1-ol, 928-96-1; bromoacetyl bromide, 598-21-0.

New Reaction of L-Ascorbic Acid: Unusual Molecular Complexes of the Product[1]

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2-Methyl-2,5-dimethoxy-2,5-dihydrofuran (**4**), a cyclic acetal of *cis*-3-acetylacrolein (**3**), reacts with L-ascorbic acid (**1**) in aqueous solution to give amorphous 2-(5-methyl-2-furyl)-3-keto-L-gulonolactone 3,6-hemiketal (**6**) as the major product. The reaction mechanism most likely involves *cis*-3-acetylacrolein, i.e., 4-keto-*cis*-2-pentenal (**3**) as an intermediate. Hemiketal **6** was converted with succinic anhydride into a crystalline molecular complex **8a**. X-ray structure determination shows that **8a** is held together by strong hydrogen bonds between the succinic carbonyl oxygens and the C-3 hydroxyls of 2 mol of hemiketal **6**. Succinimide and *N*-methylsuccinimide also give very stable molecular complexes **8b** and **8c**, while maleic anhydride and *N*-phenylsuccinimide do not form crystalline adducts with **6**. The lactone **6** and its adducts show remarkable immunomodulation and an extremely low toxicity.

Introduction

Relatively little work has focused on the chemistry of Vitamin C since its practical syntheses[2a,b] were achieved. We described recently[3] a spontaneous reaction of L-ascorbic acid (**1**) with methylglyoxal. A mixture of isomeric ene diol acetals[3,4] formed by the loss of 1 mol of water in

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(1) Fodor, G.; Sussangkarn, K.; Arnold, R.; Karle, I.; George, C. "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, D.C., August 29, 1983; American Chemical Society: Washington, D.C., 1983; ORGN 75.

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