dissolved in H_2O, Na_2HPO_4 was added, and the pH was adjusted to 7. The flocculant was centrifuged, and the precipitate was collected and recrystallized from water to give dark green/black shiny crystals (60 mg, 66%), mp >300 °C. This compound was identical by TLC (SiO_2, eluent, butanol/acetic/H_2O, 4:2:1) and UV to that obtained from the autoxidation of 1 in the presence of tyrosine: UV (pH 5, sodium acetate buffer 0.02 M) 377.6 (log ϵ 3.73), 309.8 (log ϵ 3.53), 300.0 (log ϵ 3.53), 238.2 (log ϵ 4.22), 214 (log ϵ 4.38) + 1 drop NaOH to pH >10 changes UV to 402.2 (log ϵ 3.71), 330.4 (log ϵ 3.73), 242.6 (log ϵ 4.22), 214 (log e 4.44); ^{1}H NMR (D_2O/NaOD (1 M), TSP as internal reference) δ 2.55 (1 H, dd, J = 13.74, 8.55 Hz), 2.89 (1 H, dd, J = 13.74, 4.28 Hz), 3.38 (1 H, dd, J = 8.55, 4.27 Hz), 6.54 (1 H, d, J = 8.09 Hz), 6.626 (1 H, d, J = 8.09 Hz), 6.63 (1 H, d, J = 8.09 Hz), 6.84 (1 H, d, J = 2.29 Hz), 6.89 (1 H, dd, J = 8.09, 2.29 Hz); ^{13}C NMR (D_2O/NaOD) 39.40 (t), 56.85 (d), 114.53 (d), 118.53 (d), 122.04 (d with underlying s), 123.11 (s), 127.69 (d with underlying s), 131.01 (d with underlying s), 131.40 (s), 152.90 (s), 161.77 (s), 177.04 (s), 182.06 (s). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.15; H, 4.46; N, 8.92. Found: C, 60.75; H, 4.56; N, 8.66.

On the Scope of Asymmetric Nitrile Oxide Cycloadditions with Oppolzer's Chiral Sultam. Total Syntheses of (+)-Hepialone, (−)-(1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane, and (−)-(1*S*)-7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

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Cycloadditions of nitrile oxides with acryloyl derivatives of Oppolzer's chiral sultam produce stereoisomeric Δ^2-isoxazolines in ratios of about 90/10 at 25 °C. The major diastereomers can be isolated in pure form in 70–88% yield. Syntheses of the three title natural products are used to illustrate that optically pure isoxazolines can be transformed into a wide variety of functional groups including β,γ-dihydroxy ketones, alcohols, 1,2- and 1,3-diols, 1,3,4-triols, 1,3-amino alcohols, and 1,3,4-amino diols. It is suggested that this cycloadditive strategy complements existing asymmetric aldol routes to such functionality. A novel radical ring opening was discovered when it was found racemic 5-methyl-Δ^2-isoxazolines are formed upon reduction of optically pure 5-(iodomethyl)-Δ^2-isoxazolines with tributyltin hydride at low concentration. The scope of the asymmetric cycloaddition was studied by using methacryloyl sultam **33** and crotonoyl sultam **36**. The methacryloyl sultam exhibits very low levels of asymmetric induction, and is much less reactive than a methacrylate ester model. An X-ray crystal structure of **33** suggests a reason for this behavior: the methacryloyl group deviates significantly from planarity. The crotonoyl sultam **36** provides good levels of diastereoselectivity (90/10) in the nitrile oxide cycloaddition, but regioselectivity is lacking.

Introduction

Δ^2-Isoxazolines are central intermediates in a strategy to prepare heteroatom-substituted carbon chains that is based on cycloaddition.[1] Most Δ^2-isoxazolines are easily prepared by olefin/nitrile oxide cycloadditions,[2] are stable to many common synthetic transformations, and can be converted to a wide variety of functional groups under mild conditions. In addition, the relative stereochemistry of functional groups adorning the Δ^2-isoxazoline nucleus can often be strictly controlled.[3] These assets have generated a need for practical methods to prepare optically pure Δ^2-isoxazolines.[4]

We recently reported that the acrylamide **2** derived from Opplozer's chiral sultam **1**[5] gives good levels of asymmetric induction in nitrile oxide cycloadditions (eq 1).[6] Although the degree of selectivity observed (85/15 to 95/5) is not outstanding when judged against transformations like enolate alkylations and Lewis acid catalyzed Diels–Alder reactions (which often occur at low temperature), it is quite high when compared to existing asymmetric nitrile oxide cycloadditions in particular,[4] and to other types of thermal additions in general.[3] This work also resulted in the development of a new model for the thermal addition and cycloaddition reactions of **2** (Figure 1).[6,7] In this model, the reagent (in this case, a nitrile oxide) attacks the β-face of the low-energy conformer of **2**. We also demonstrated that adducts **3** could be separated without difficulty and that the major diastereomers could be reductively cleaved with L-Selectride (Aldrich) to give optically pure isoxazolines **4**, along with recovered sultam **1**.

This paper describes the results of a study that we undertook to determine usefulness of this asymmetric nitrile oxide cycloaddition. Three natural products, (+)-hepial-

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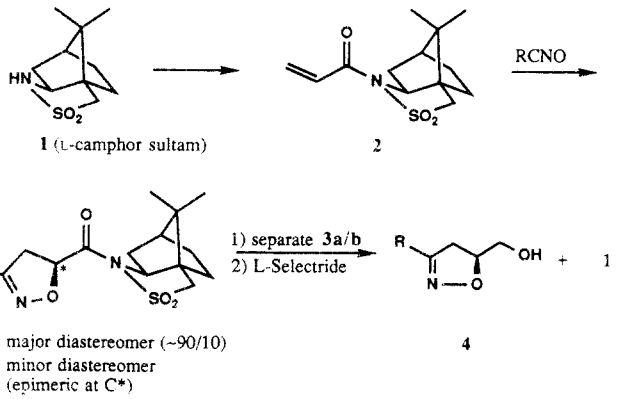
(4) (a) Kametani, T.; Huang, S.-P.; Yokahoma, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060. (b) Olsson, T.; Stern, K.; Sundell, S. *J. Org. Chem.* **1988**, *53*, 2468. (c) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137.

(5) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969, see especially Section 3.3. The original printing of this excellent review contains printer errors. A version is reprinted in the Errata section of *Tetrahedron* **1987**, *43*, issue 18.

(6) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555.

(7) Oppolzer, W.; Poli, G.; Starkmann, C.; Bernardelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559.

0022-3263/90/1955-4585$02.50/0



one, (−)-(1*R*,3*R*,5*S*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]-nonane, and (−)-(1*S*)-7,7-dimethyl-6,8-dioxabicyclo-[3.2.1]octane were selected as simple yet representative targets to determine the generality of the cycloaddition, to develop new methods to remove the chiral auxiliary, and to illustrate how some common functional group patterns could be directly prepared in optically active form. To determine the scope of the method with respect to acrylate substitution, we studied the cycloadditions of methacrylate and crotonate derivatives of 1.

Results and Discussion

Syntheses with Acryloyl Sultam (2). The chiral auxiliaries (−)-1 and (+)-1 were initially prepared by Oppolzer's procedure;[8] however, both became commercially available during the course of our study. All of the total syntheses required acrylate derivative **2**, which was reproducibly prepared in 56% yield by deprotonation of (+)-1 (L-2,10-camphor sultam) with NaH in toluene, followed by addition of acryloyl chloride and a catalytic amount of copper(I) chloride.[9] Other conditions for acryloylation gave significantly lower yields of **2**.

(+)-Hepialone (5) is a sex pheromone that was isolated in trace amounts by Kubo et al. in 1984 from the hair-pencils of the male moth *Hepialis californicus Bvd.*[10] It has been synthesized in both racemic and optically active form.[11] Our purposes in selecting hepialone as a target were (1) to illustrate that functionalized β-hydroxy ketones could be prepared in optically pure form and (2) to illustrate that the chiral auxiliary could ultimately be replaced by a C–C bond. Figure 2 shows that the synthesis of the precursor of hepialone **6** is representative of how one might prepare a wide variety of β-hydroxy ketones of the general type **7**.

The synthesis of (+)-hepialone is outlined in Scheme I. Treatment of bromo ketal **8**[12] with sodium nitrite[13] provided nitro ketal **9** in 31% yield after purification by

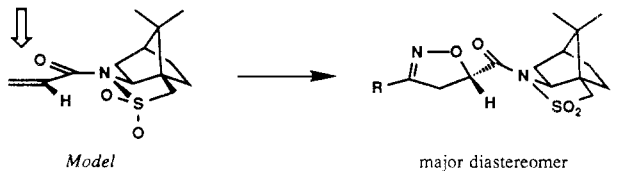


Figure 1.

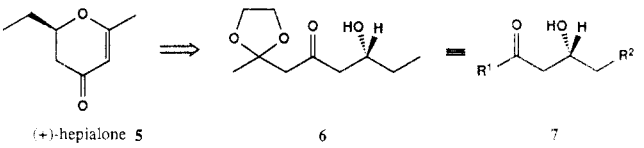


Figure 2.

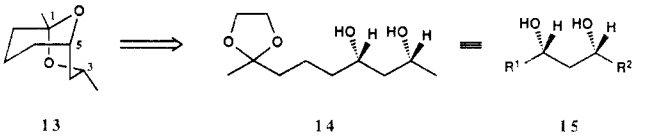


Figure 3.

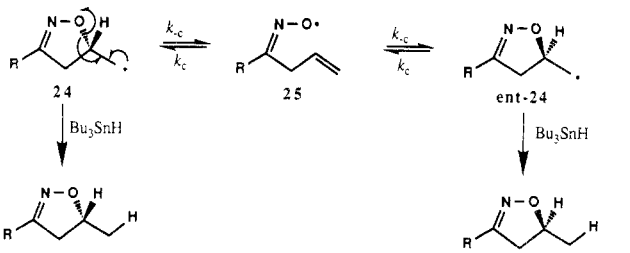


Figure 4.

vacuum distillation. Multigram quantities of **9** were easily prepared despite the low yield. The cycloaddition of **9** with **2** was conducted by the Mukaiyama method[14] (PhNCO, benzene, 25 °C, 48 h) and gave an 88/12 mixture of **10a** and **10b**. The major diastereomer **10a** was completely separated from **10b** by flash chromatography (2–3-g scale) and was isolated in 85% yield. Reduction of **10a** with L-Selectride gave an 85% yield of alcohol **11**, along with recovered sultam **1**. Coupling of the mesylate or iodide derivatives of **11** with a variety of lower and higher order cuprates did not provide a satisfactory route to **12**; however, the tosylate derivative of **11** did couple with lithium dimethyl cuprate to provide **12** in 57% purified yield.[15] Standard Raney nickel reduction[16] of **12** (H_2, boric acid, $MeOH/H_2O$) gave **6** in 88% yield. Brief exposure of **6** to 3 N HCl gave (+)-hepialone (**5**). Our sample was spectroscopically and chromatographically identical with a sample of (+)-**5** kindly provided by Professor Kamikawa.[17] Our rotation (+212°, *c* = 0.67, EtOH) was slightly lower than the highest reported rotation (+236°) of hepialone.[11b,e]

***endo*-7,7-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (13)** is a host specific substance for an ambrosia beetle that infests the bark of the Norway Spruce.[18] Although both

(8) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035.
(9) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
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(12) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.
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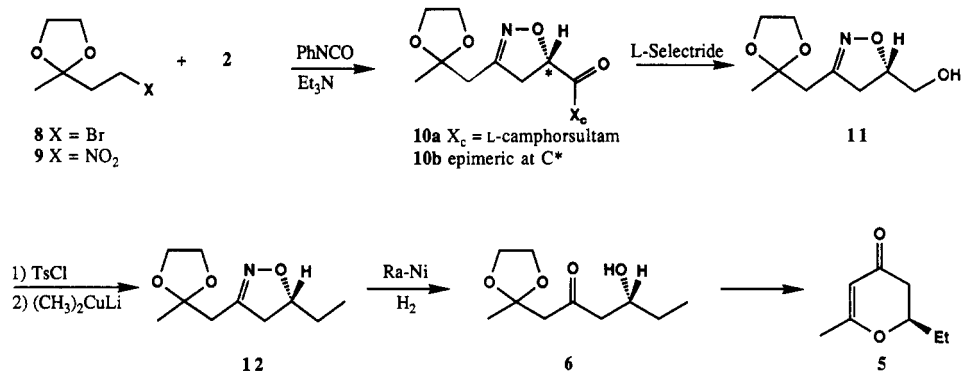
(14) Makaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
(15) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.
(16) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.
(17) We thank Professor Kamikawa for kindly providing spectra and a sample of (−)-hepialone. We note that the ^{13}C NMR originally reported for hepialone (ref 10) is different from the spectra of all of the synthetic products (including ours). While we were not able to obtain an authentic sample, our product was identical with Professor Kamikawa's product, which, in turn, was directly compared with the natural product. Since all other spectra are in accord, we suspect that the original ^{13}C spectrum of natural hepialone must have been recorded in a solvent other than $CDCl_3$.

Scheme I



Scheme II

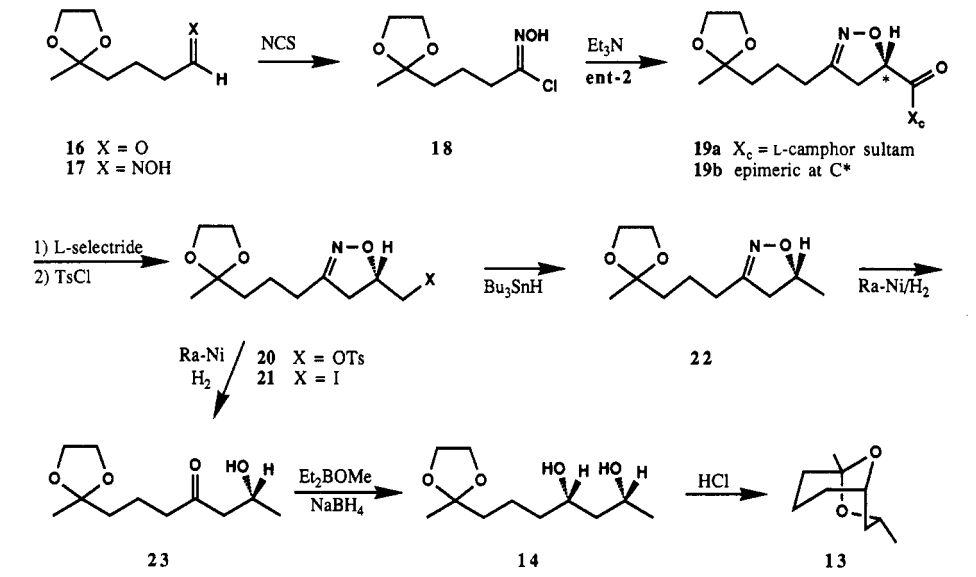


Table I. Reductions of 21

entry	[21], M	temp, °C	$[\alpha]_D$ 22, deg	% ee 22[a]	$[\alpha]_D$ 23, deg	% ee 23[b]	% de of MTPA
1	0.045	85	+2.4	4	−2.3	5	20
2	0.080	80	+8.8	15	*c*	*c*	*c*
3	0.450	80	+27.0	46	*c*	*c*	*c*
4	neat	80	+40.8	69	−33.3	73	90
5	neat	150	+31.2	52	*c*	*c*	*c*
6	neat	50	+48.8	83	−37.6	83	90
7		direct Ra-Ni reduction of 21 to 23			−45.5	>98	>98

[a] Calculated by assuming that product from entry 6 is 83% ee. [b] Calculated by assuming that −45.5° is the maximum rotation. [c] Experiment not conducted.

enantiomers have been prepared,[19] the absolute stereochemistry of the natural product is still not known with certainty.[19c] In preparing (−)-**13** (Figure 3), we illustrate how optically active *syn*-1,3-diols (**14**, **15**) can be prepared, and we introduce a method for complete reductive removal of the chiral auxiliary (that is, conversion to a methyl group). β-Hydroxy ketones can also be reduced to *anti*-1,3-diols, so both *syn*- and *anti*-diols are available by this route.

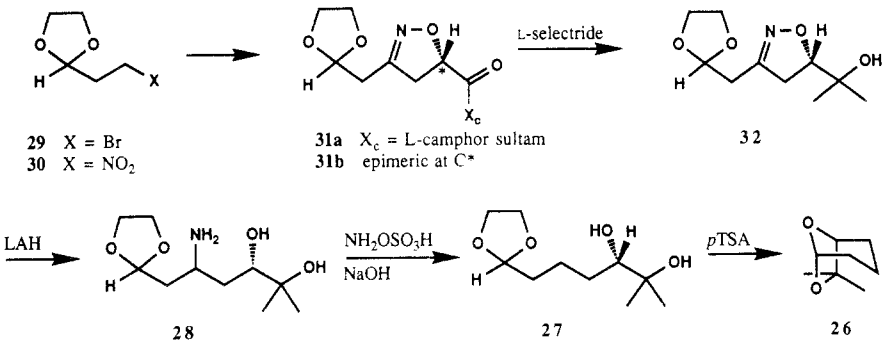
The synthesis of (−)-**13** is illustrated in Scheme II. Ethyl 5-oxohexanoate was converted to aldehyde **16** in good yield by using standard procedures (see the Experimental Section). Hydroxamination of **16** gave **17**. Conversion of **17** to oxime chloride **18**, followed by cycloaddition with **2** by the Huisgen method[20] (Et_3N, Et_2O, 25 °C), gave **19a**/**19b** in a ratio of 92/8. The desired isomer **19a** was isolated by chromatography in 89% yield. Standard L-Selectride reduction of **19**, followed by tosylation, gave **20**. Tosylate **20** was then reduced by the method of Ueno[21] (NaI, 0.045

(18) (a) Heemans, V.; Francke, W. *Naturwissenschaften* **1976**, *63*, 344. (b) Vite, J. P.; Franke, W. *Ibid.* **1976**, *63*, 550.

(19) (a) Adams, J.; Frenette, R. *Tetrahedron Lett.* **1987**, *28*, 4773. (b) Ohta, H.; Ozaki, K.; Tsuchihashi, G. *Chem. Lett.* **1987**, 2225. (c) Redlich, H.; Schneider, B.; Hoffmann, W.; Geueke, K.-J. *Justus Liebigs Ann. Chem.* **1983**, 393. (d) Gerlach, H.; Kunzler, P. *Helv. Chim. Acta* **1977**, *60*, 638. (e) Redlich, H.; Schneider, B.; Francke, W. *Tetrahedron Lett.* **1980**, *21*, 3013. (f) Sato, T.; Itoh, T.; Hattori, C.; Fujisawa, T. *Chem. Lett.* **1983**, 1391. (g) Kongkathip, B.; Kongkathip, N. *Tetrahedron Lett.* **1984**, *25*, 2175. (h) Nakata, T.; Nagao, S.; Takao, S.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 73. (i) Guindon, Y.; St-Denis, Y.; Daigneault, S.; Morton, H. E. *Tetrahedron Lett.* **1986**, *27*, 1237. (j) Mohr, P.; Tamm, C. *Tetrahedron Lett.* **1987**, *28*, 395. (k) Bernardi, R.; Ghiringhelli, D. *J. Org. Chem.* **1987**, *52*, 5021. (l) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419. (m) Pauphin, G.; Fauve, A. Veschanbre, H. *J. Org. Chem.* **1989**, *54*, 2238. (n) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, *27*, 3535.

(20) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.

Scheme III



M Bu_3SnH, DME, 80 °C, 2 h). This procedure is a radical reduction of an in situ generated iodide **21**. To our surprise, the deoxygenated product **22** exhibited a very low rotation (+2.4°) for compounds in this series. The same low-rotating **22** was obtained when iodide **21** was prepared and independently subjected to tin hydride reduction. That racemization had actually occurred was confirmed by Raney nickel reduction of **22** to the known ketone **23**;[19] our sample had a much lower rotation than the literature value.[19c]

A series of tin hydride reductions conducted at varying concentrations and temperatures quickly established that the racemization was occurring at the stage of an intermediate radical. These experiments are summarized in Table I. To assess the degree of racemization, several of the scalemic (partially optically pure) samples of **22** were reduced to **23**, and the optical purity of these samples was assessed by rotation and by formation of MTPA esters[22] (see the Experimental Section). As the concentration of the tin hydride increases, the amount of racemization decreases (see entries 1–4). In neat tin hydride at 80 °C, **22** was produced with about 69% ee. A brief temperature study (entries 4–7) showed that decreasing the reaction temperature increased the optical purity, and at 50 °C, the sample of **22** that was obtained approached an acceptable level of optical purity (83%).

Figure 4 illustrates a mechanism for racemization that is consistent with the experimental observations. Direct reduction of **24** competes with its ring opening to give achiral **25**. β-Oxygen-substituted radicals do not usually fragment; however, **25** is reminiscent of a nitroxyl radical, and its relative stability undoubtedly contributes to the tendency of **24** to undergo reverse cyclization.[23] The data from Table I can be used to calculate[24] a rate constant for opening of **24**; however, an inspection of this data shows that, even though the qualitative trends are clear, the quantitative agreement of the various methods to estimate the enantiomeric excess of **22** is not good. Given this level of error, about the best we can say at present is that k_{-c} probably lies in the range of 10^5–10^7 s^{-1}.

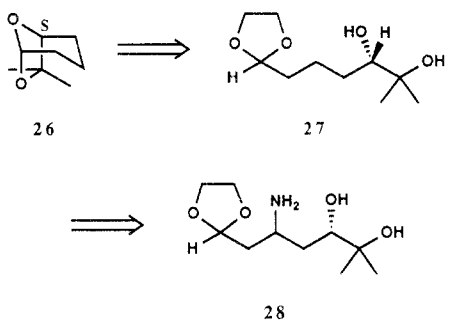


Figure 5.

A shorter route to optically pure **23** was opened by the discovery that **21** could be directly reduced with Raney nickel (25 °C, 16 h, H_2, boric acid, $MeOH/H_2O$). The hydroxy ketone **23** obtained by this route showed the highest rotation yet reported for this compound, and its derived MTPA ester was a single diastereomer according to ^1H and ^{19}F NMR analysis.[22] TLC evidence[25] indicated that the isoxazoline was first reduced to a β-hydroxy ketone and then reductive deiodination followed. Thus, there is no opportunity for racemization. Known, syn-selective reduction of **23** gave diol **14** in 86% yield.[26] (−)-(1*R*,3*R*,3*S*)-**13** was formed on exposure of **14** to 3 N HCl and was isolated in 57% yield after chromatographic purification. The rotation of this sample (−46.2°) was marginally higher than the past rotations,[19] and we believe that the sample is optically pure.

(+)-(1*S*)-7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (26) is an aroma constituent of beer[27] that was isolated from hop oil in 1967 by Naya and Kotake.[28] It has been synthesized from tartaric acid.[29] As illustrated in Figure 5, the synthesis of (+)-**26** was undertaken to demonstrate (1) that products lacking the isoxazoline nitrogen atom (see **27**) could be prepared, (2) that optically active 1,3-amino alcohols (see **28**) could be prepared, and (3) that the chiral auxiliary could be removed by a method other than L-Selectride reduction.

The synthesis of (+)-**26** is illustrated in Scheme III. Functionalized nitro compound **30** was prepared from readily available **29** on multigram scale, albeit in 18%

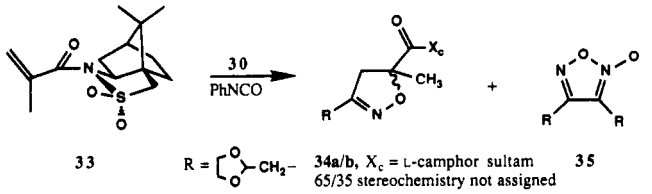
(21) Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* **1983**, 795.
(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(23) Reviews with references to reversible radical cyclizations: (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press, New York, 1980; Vol. 1, pp 162–283. (b) Surzur, J.-M. In *Reactive Intermediates*, Abramovitch, R. A., Ed.; Plenum Press, New York; 1982; Vol. 2, Chapter 3. Aminyl radical cyclizations have recently been shown to be reversible: (c) Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528.
(24) The following equation was derived from the mechanism in Figure 4 to calculate k_{-c}.

$$k_{-c} = 2k_H[Bu_3SnH]_{eff}/(R/S - 1)$$

where R/S = % retention/% inversion

(25) After 1 h of reduction, isoxazoline **21** was consumed, and a single new spot appeared which was not identical with **22**, and which developed to the characteristic blue-green color of a β-hydroxy ketone when exposed to *p*-anisaldehyde spray. Over 15 h, this spot was replaced by the spot for **23**.
(26) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(27) Tressl, R.; Friese, L.; Endesack, F.; Koeppler, H. *J. Agric. Food Chem.* **1978**, *26*, 1422.
(28) Naya, Y.; Kotake, M. *Tetrahedron Lett.* **1967**, 2459.
(29) Masaki, Y.; Nagata, K.; Serizawa, Y.; Kaji, K. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1983**, *26*, 545; *Chem. Abstr.* **1983**, *101*, 23162x.

Scheme IV



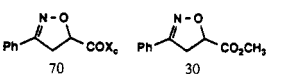
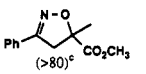
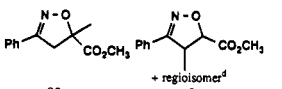
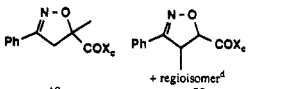
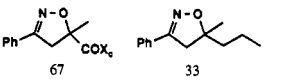
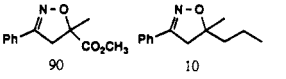
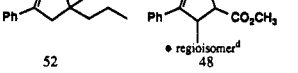
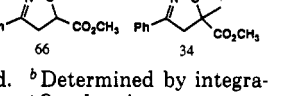
isolated yield. Cycloaddition of **30** with **2** by the Mukaiyama method gave **31a/b** in a ratio of 85/15. Flash chromatography gave pure **31a** in 70% yield. Addition of excess methylmagnesium bromide to **31a** gave tertiary alcohol **32**, along with recovered **1**. Reduction of **32** with LAH according to the procedure of Jäger[30] gave amino alcohol **28** in 97% crude yield. Compound **28** was largely a single stereoisomer, but its relative stereochemistry was not rigorously assigned.[31] Jäger has shown that reductions of isoxazolines to amino alcohols are often stereoselective,[30] and our method for making optically active isoxazolines could easily be integrated with Jäger's reductions to give a wide assortment of optically active amino alcohols. In the case at hand, the crude amino alcohol **28** was deaminated by a modification of a literature method.[32] After chromatography, pure diol **27**, lacking all vestiges of the isoxazoline nitrogen, was isolated in 54% yield. Treatment of **27** with *p*-TSA in benzene produced (+)-**26** in 61% isolated yield.

Scope of the Asymmetric Cycloaddition. Methacryloyl and Crotonoyl Sultams 33 and 36. The second goal of this research was to determine the scope of the cycloaddition with respect to substituent tolerance on the chiral sultam. As a model for a 2-substituted acrylate, methacryloyl sultam **33** was prepared in 96% yield by acylation of **1** (see Scheme IV). When **33** was reacted with nitro compound **30** (Mukaiyama method), a mixture of diastereomers **34a/b** was isolated in 86% yield in a ratio of 65/35. Although the major isomer was isolated in pure form (56%), we were not able to rigorously determine its stereochemistry based on spectra alone. In view of the low level of selectivity, other methods of structure assignment were not pursued.[33,34] Not only is **33** less selective than **2**, it is also significantly less reactive. For example, cycloadditions of **2** could be conducted for 1–3 days at room temperature, while those of **33** required similar time periods at 80 °C for completion. Also, even though the cycloadducts **34a/b** were isolated in good yield, significant amounts (>10%) of the nitrile oxide dimer, bis(2-dioxanylethyl)furoxan (**35**), were detected. In contrast, crude yields of cycloadducts with **2** approached the quantitative level, and nitrile oxide dimers were not observed.

1,1-Disubstituted olefins (like **33**) are known to be less reactive than 1-substituted olefins (like **2**), but we suspected that **33** was less reactive than it should be based on this substituent effect alone. A series of simple competition experiments confirmed this suspicion. The data for these competitions are collected in Table II. In each competition, two olefins (2 equiv each) were allowed to compete for benzonitrile oxide (generated in situ by the Huisgen method), and the ratio of cycloadducts was measured by ^{1}H NMR integration of the crude reaction mixture. Methyl esters were selected as achiral models, and reference samples of all of the pure cycloadducts were prepared by standard cycloadditions.

From these experiments, a reactivity scale can be constructed as outlined in Figure 6. Because the competition experiments were not conducted under ideal conditions for kinetic analysis, we emphasize the approximate nature of this scale. Although the trends are secure, slightly different relative rates are calculated by selecting different

Table II. Competitive Rate Studies of a Series of Dipolarophiles toward Nitrile Oxide Cycloaddition

entry	olefin 1	olefin 2	[Ph—C≡N⁺—O⁻][a]	cycloadducts (% ratio)[b]
1				 70 30
2				 (>80)[c]
3				 92 + regioisomer[d] 8
4				 48 + regioisomer[d] 52
5				 67 33
6				 90 10
7				 52 • regioisomer[d] 48
8				 66 34

[a] Generated by the Huisgen method. [b] Determined by integration of the crude ^{1}H NMR spectrum. [c] Overlapping resonances precluded accurate integration of the minor product peaks. [d] See Scheme V.

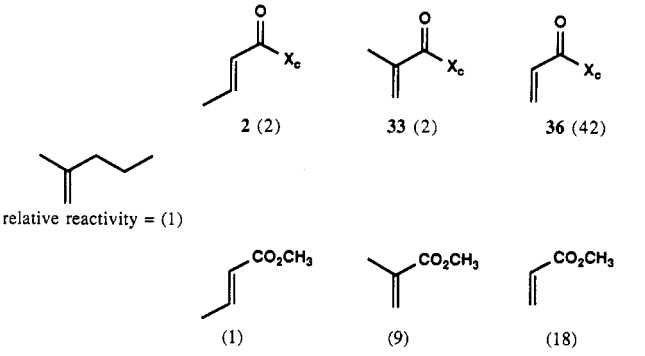


Figure 6.

(30) Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601.

(31) Large C5 substituents on the isoxazoline usually promote formation of syn amino alcohols; however, we cannot rule out a possible reduction to the anti amino alcohol that is directed by the hydroxy group (see ref 30).

(32) Doldouras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, *100*, 341.

(33) Oppolzer has noted decreased reactivity and reduced stereoselectivity for osmylations (ref 34a) and catalytic hydrogenations (ref 34b) of related tigloyl sultams. We cannot assign our stereostructures by analogy because the osmylation of a tigloyl sultam gives modest selectivity that is in the same direction as osmylation of the acryloyl sultam, but hydrogenation of the two sultams gives opposite selectivities.

(34) (a) Opplzer, W.; Barras, J.-P. *Helv. Chim. Acta* **1987**, *70*, 1666. (b) Oppolzer, W.; Poli, G. *Tetrahedron Lett.* **1986**, *27*, 4717.

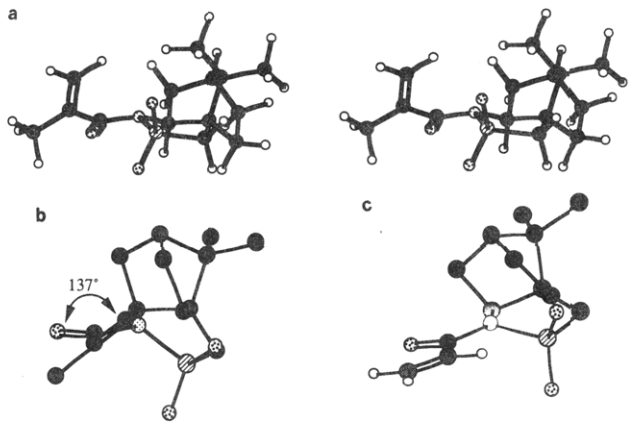


Figure 7. (a) Stereoview of the crystal structure of **33**. (b) View of **33** looking down the methacryloyl C–C single bond. Hydrogen atoms are omitted. (c) View of **2** looking down the acryloyl C–C single bond. Only vinyl hydrogens are shown.

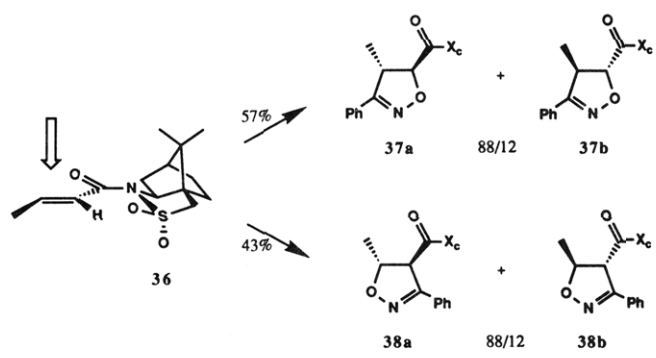
reference reactions. Nonetheless, when cross-checks are possible, they are reasonably consistent.

The trends observed with the ester models simply reproduce the known reactivity patterns of alkenes in nitrile oxide cycloadditions:[2] activated, monosubstituted > activated, 1,1-disubstituted > unactivated 1,1-disubstituted ≈ activated, trans-1,2-disubstituted. The data reveal that acryloyl-**2** and crotonoyl sultams **36** are marginally more reactive than their model esters, perhaps because the activating substituent is slightly more electronegative.[35] More interesting is the relative reactivity pattern within the sultam series. While the relative reactivity of the acryloyl sultam **2** compared to the crotonoyl sultam **36** parallels the ester model (acryloyl is about 20 times more reactive than crotonoyl), methacryloyl sultam **33** is about 9 times less reactive than the ester model would indicate. Indeed, the activating effect of the acyl substituent is almost completely lost, as **33** is only marginally more reactive than the unactivated, 1,1-disubstituted olefin (see Table II, entry 5).

An X-ray crystal structure of **33** suggested reasons for its reduced reactivity and its reduced stereoselectivity.[36] A stereographic representation of this structure is shown in Figure 7. The geometry about the conjugated alkene of **33** is much different from acryloyl and crotonoyl sultams.[37] These latter derivatives all orient their alkenes in a planar, s-cis arrangement (see Figure 7c) with the small hydrogen in the sterically demanding location. Substitution of this hydrogen by an alkyl group introduces a severe steric interaction in the planar, s-cis form, and the planar s-trans form offers no improvement. Sulfonamide C–N rotamers have unfavorably aligned dipoles. Thus, **33** has no good planar conformation, and, in the solid state, it opts for a nonplanar conformation in which the alkene is s-trans-like (see Figure 7c).[36] The O=C—C=C dihedral angle is 137°.

Although we can conclude nothing about the geometry of **33** in the transition state of the dipolar cycloaddition, we can assume that the reactive conformers are probably not planar for the same reasons that ground-state conformers are not planar. Thus, the stereoselectivity of **33** may decrease either because multiple conformers with differing facial selectivities are involved, or, if a single conformer is involved (as proposed for **2**), because its face selectivity is poor. The reduced reactivity of **33** also has two possible origins: nonplanar activating substituents may be less electronically activating than planar ones due to reduced conjugation of the amide, or the sulfonamide oxygen or nitrogen (depending on the face of attack) may retard the approach of a nitrile oxide more when the amide is twisted out of the plane of the alkene than when it is planar. That **33** is about equal in reactivity with the model unactivated olefin may be construed as supporting the electronic argument, but this equality could be a coincidence.

Scheme V



Cycloadditions of nitrile oxides with activated disubstituted olefins like crotonates generally produce mixtures of regioisomers[2] (see Table II, entry 3). Unfortunately, crotonoyl sultam **36** is no different in this regard (see Scheme V). The cycloaddition of **36** with benzonitrile oxide gave a mixture of four products, the ratio of which could be determined by careful inspection of the crude ^1H NMR spectrum. The structures of the products were assigned after careful chromatographic separation. The regioisomers **37a/b** and **38a/b** were formed in a ratio of 57/43. Within each regioisomeric pair was a pair of stereoisomers (**a/b**) that was formed in a ratio of 88/12. Because crotonates and acrylates have similar conformations, and because they produce similar levels of selectivity, we feel secure in assigning stereochemical outcome of the reactions of **36** by analogy to **2**. It is interesting that the facial selectivity is independent of the regiochemical orientation of the approaching nitrile oxide.

Conclusions

This research is part of a larger program to develop the isoxazoline-based cycloadditive strategy for preparing heteroatom-substituted carbon chains into a general complement to the omnipresent aldol strategy.[1a] We have provided simple illustrations of the many kinds of molecules that can be prepared in optically active form by using derivatives of Oppolzer's chiral sultam in the cycloadditive strategy.

Cycloadditions of nitrile oxides with acryloyl sultam **2** generally exhibit good levels of diastereoselection (85/15 to 92/8 in this work). The major product is separable from its isomer, and the overall recovery is so good that its yield often approaches the maximum permitted by the diastereomer ratio. The chiral auxiliary can then be cleaved by reduction or nucleophilic addition to yield optically pure, unsubstituted or substituted 5-(hydroxymethyl)-Δ^2-isoxazolines. In turn, these isoxazolines are precursors of a wide variety of molecules including β-hydroxy ketones, β,γ-dihydroxy ketones, alcohols, 1,2- and 1,3-diols, 1,3,4-

(35) It is also interesting to compare the reactivity of the individual faces of **2**. The β-face of **2** is about 5 times more reactive than a face of methyl acrylate while the α-face is about half as reactive.

(36) During the course of our work, Oppolzer reported the crystal structure of a tigloyl sultam which has a similar orientation to **33** (see ref 7).

(37) (a) Bernardinelli, G.; Oppolzer, W.; Schneider, P. *Acta Crystallogr., Sect. C* **1987**, *43*, 1000. (b) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397.

triols, 1,3-amino alcohols, and 1,3,4-amino diols. By integrating other known transformations of isoxazolines[1] with this chemistry, even more possibilities arise.

Methacryloyl sultam **33** provides relatively low levels of asymmetric induction (although the isomers are separable), and there is currently no generally useful methacrylate chiral auxiliary for nitrile oxide cycloadditions. Crotonoyl sultam **36** is unacceptable not because stereoselectivity is low but because regioselectivity is low. Fortunately, the Jäger alkylation[1b] is an excellent method to convert 5-substituted isoxazolines into trans-4,5-disubstituted isoxazolines. Thus, although we provide no examples, it is clear that optically active trans-4,5-disubstituted Δ^2-isoxazolines could be prepared by a straightforward extension of this work.

The advent of a general method to prepare many important types of Δ^2-isoxazolines in optically pure form should greatly extend the usefulness of the cycloadditive strategy. Concurrent with this research, we have developed new methods to control relative stereochemistry about isoxazolines, and these methods will be reported shortly.

Experimental Section[38]

[3a*R*-(3aα,6α,7aβ)]-Hexahydro-8,8-dimethyl-1-(1-oxo-2-propenyl)-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (2). To a suspension of dry, oil-free NaH (0.50 g, 20.9 mmol) and toluene (90 mL) was added L-2,10-camphorsultam **1** (3.00 g, 13.9 mmol). After 1 h at 25 °C, CuCl (138 mg, 1.39 mmol) was added, followed by acryloyl chloride (2.26 mL, 27.8 mmol). After 22 h, the reaction mixture was slowly quenched with H_2O (8 drops) and then concentrated under reduced pressure. The residue was extracted into EtOAc (100 mL) and passed through silica gel. The filtrate was concentrated under reduced pressure and purified by chromatography using Waters Prep 500 (18:82 EtOAc/hexane). The solvent was removed under reduced pressure to yield pure **2** (2.10 g, 56%): ^{1}H NMR ($CDCl_3$) δ 0.98 (3 H, s), 1.17 (3 H, s), 1.39 (2 H, s), 1.90 (3 H, m), 2.14 (2 H, m), 3.45 (1 H, d, J = 13.8 Hz), 3.53 (1 H, d, J = 13.8 Hz), 3.94 (1 H, dd, J = 7.2, 5.4 Hz), 5.86 (1 H, dd, J = 10.3, 1.3 Hz), 6.50 (1 H, dd, J = 16.6, 1.3 Hz), 6.87 (1 H, dd, J = 16.7, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.8, 26.5, 32.8, 38.4, 44.7, 47.8, 48.6, 53.1, 65.1, 127.8, 131.3, 163.8; IR (thin film) 2963, 1674, 1329, 1273, 1238 cm^{-1}; MS m/z 269 (M^+), 190, 162, 55; high-resolution MS calcd for $C_{13}H_{19}NO_3S$ 269.1086, found 269.1085.

2-Methyl-2-(2-nitroethyl)-1,3-dioxolane (9).[13] A solution of bromo ketal[12] **8** (32.0 g, 0.165 mol), $NaNO_2$ (22.8, 0.330 mol), and DMF (200 mL) was stirred at 25 °C for 48 h. The reaction mixture was poured into H_2O (500 mL) and extracted with ether (4 × 200 mL). The extracts were washed with H_2O (4 × 200 mL) and dried over $MgSO_4$. Concentration of the residue under reduced pressure and distillation afforded a clear liquid (8.25 g, 31%), bp 70–75 °C (0.5 mmHg): ^{1}H NMR ($CDCl_3$) δ 1.31 (3 H, s), 2.43 (2 H, t, J = 6.9 Hz), 3.93 (4 H, m), 4.43 (2 H, t, J = 6.9 Hz).

[3a*R*-[1(*S),3aα,6aα,7aβ]]-1-[[4,5-Dihydro-3-[(2-methyl-1,3-dioxolan-2-yl)methyl]-5-isoxazolyl]carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (10a).** To a solution of *N*-acryloyl camphor sultam **2** (2.10 g, 7.8 mmol), nitro ketal **9** (2.76 g, 17.2 mmol), and benzene (210 mL) at 25 °C and under N_2 was added PhNCO (2.54 mL, 23.4 mmol) followed by Et_3N (2.40 mL, 17.2 mmol). After 24 h, PhNCO (2.54 mL, 23.4 mmol) and Et_3N (2.40 mL, 17.2 mmol) were added. After an additional 24 h, the reaction mixture was diluted with EtOAc (300 mL), washed with H_2O (300 mL), and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by chromatography (35:65 EtOAc/hexane). Removal of the solvent under reduced pressure gave the major diastereomer **10a** as a thick gum (2.73 g, 85%): ^{1}H NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.14 (3 H, s), 1.32 (3 H, s), 1.35 (2 H, m), 1.85 (3 H, m), 2.06 (2 H, m), 2.64 (1 H, d, J = 14.0 Hz), 2.72 (1 H, d, J = 14.0 Hz), 3.26 (1 H, dd, J = 17.9, 11.1 Hz), 3.42 (1 H, d, J = 13.9 Hz), 3.43 (1 H, dd, J = 17.9, 6.6 Hz), 3.51 (1 H, d, J = 13.8 Hz), 3.91 (1 H, m), 3.93 (4 H, s), 5.45 (1 H, dd, J = 11.1, 6.6 Hz); IR (thin film) 2961, 2886, 1700, 1381, 1333, 1273, 1239, 1167, 1136, 1069, 1048, 916, 870, 733 cm^{-1}; $[\alpha]^{25}_D$ +204° (c 10.5, $CHCl_3$); MS m/z 397 (M − 15), 242, 170, 135, 126, 87; high-resolution MS calcd for $C_{18}H_{25}N_2O_6S$ 397.1433, found 397.1432.

(*S*)-4,5-Dihydro-3-[(2-methyl-1,3-dioxolan-2-yl)methyl]-5-isoxazolemethanol (11). To a solution of isoxazoline **10a** (2.54 g, 5.94 mmol) and THF (240 mL) at 25 °C under N_2, was added a 1 M solution of L-Selectride in THF (14.8 mL, 14.8 mmol) over 30 s. After 30 min, the reaction mixture was quenched slowly with H_2O (2.45 mL). Aqueous NaOH (15%, 2.45 mL) was added followed by 30% H_2O_2 (2.45 mL). The solution was diluted with EtOAc (300 mL) and then dried over $MgSO_4$. The residue was concentrated under reduced pressure and purified by chromatography (80:20 EtOAc/hexane). Removal of the solvent under reduced pressure afforded **11a** as a thick oil (1.01 g, 85%): ^{1}H NMR ($CDCl_3$) δ 1.34 (3 H, s), 2.27 (1 H, bs), 2.65 (1 H, d, J = 14.1 Hz), 2.71 (1 H, d, J = 14.1 Hz), 2.92 (1 H, dd, J = 17.5, 7.6 Hz), 3.05 (1 H, dd, J = 17.5, 10.7 Hz), 3.53 (1 H, dd, J = 12.1, 4.7 Hz), 3.73 (1 H, dd, J = 12.1, 3.2, Hz), 3.95 (4 H, m), 4.65 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 23.8 (q), 37.0 (t), 39.1 (t), 63.4 (t), 64.5 (t), 64.6 (t), 80.4 (d), 108.2 (s), 155.9 (s); IR (thin film) 3422 (vb), 2984, 2932, 2890, 1653, 1622, 1559, 1507, 1437, 1381, 1352, 1215, 1129, 1094, 1044, 951 cm^{-1}; $[\alpha]^{25}_D$ +114° (c 4.0, ($CHCl_3$); MS m/z 186 (M − 15), 126, 87, 43; high-resolution MS calcd for $C_8H_{12}NO_4$ 186.0761, found 186.0761.

(*S*)-4,5-Dihydro-3-[(2-methyl-1,3-dioxolan-2-yl)methyl]-5-isoxazolemethanol 4-Methylbenzenesulfonate Ester. To a solution of alcohol **11** (305 mg, 1.51 mmol), *p*-toluenesulfonyl chloride (375 mg, 1.97 mmol), and CH_2Cl_2 (8 mL) was added Et_3N (296 mL, 2.12 mmol) followed by DMAP (9 mg, 0.075 mmol). After 26 h at 25 °C, the reaction mixture was concentrated under reduced pressure. The mixture was dissolved in ether and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (50:50 EtOAc/hexane), and the solvent was removed under reduced pressure to afford a white film (540 mg, 100%): ^{1}H NMR ($CDCl_3$) δ 1.33 (3 H, s), 2.45 (3 H, s), 2.66 (1 H, d, J = 14.2 Hz), 2.72 (1 H, d, J = 14.2 Hz), 2.99 (1 H, dd, J = 17.7, 6.7 Hz), 3.13 (1 H, dd, J = 17.7, 10.6 Hz), 3.97 (4 H, m), 4.02 (2 H, m), 4.73 (1 H, m), 7.36 (2 H, d, J = 8.6 Hz), 7.79 (2 H, d, J = 8.6 Hz).

(*R*)-5-Ethyl-4,5-dihydro-3-[(2-methyl-1,3-dioxolan-2-yl)-methyl]isoxazole (12).[15] A solution of 1.5 M CH_3Li/LiBr in ether (417 mL, 0.626 mmol) was added to a suspension of CuI (57 mg, 0.298 mmol) and ether (2 mL) under N_2 at −5 °C. After 30 min, a solution of the above tosylate (53 mg, 0.149 mmol) in ether (5 mL) was added dropwise. After 18 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and the residue was extracted with ether (3 × 20 mL). The extracts were dried over $MgSO_4$, and the solution was concentrated under reduced pressure. Purification of the residue by chromatography (25:75 EtOAc/hexane) and removal of the solvent under reduced pressure afforded **12** as an oil (17 mg, 57%): ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.3 Hz), 1.36 (3 H, s), 1.57 (1 H, m), 1.69 (1 H, m), 2.68 (1 H, dd, J = 17.1, 8.1 Hz), 2.70 (2 H, s), 3.06 (1 H, dd, J = 17.1, 10.4 Hz), 3.98 (4 H, m), 4.50 (1 H, m); ^{13}C NMR

(38) **General.** All melting points and boiling points are uncorrected. The materials obtained from commercial suppliers were used without further purification. Reagents and solvents were purified as follows: Et_3N, DMF, CH_2Cl_2, and toluene were distilled from CaH_2; benzene, THF, and ether were distilled from sodium/benzophenone; and EtOAc and hexane were distilled and stored in 4-L bottles. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Model WH-300 (300 MHz for ^{1}H; 75 MHz for ^{13}C). Chemical shift values are in parts per million (δ) downfield from tetramethylsilane as an internal reference at 0.0000 ppm. Infrared spectra (cm^{-1}) were obtained on a Perkin-Elmer Model IR/32 (FT-IR) spectrometer using NaCl plates or 0.2 mm path NaCl microcavity cells as indicated. Low-resolution mass spectra were obtained on an LKB-9000 instrument. High-resolution mass spectra were obtained by peak matching on a Varian MATCH-5DF instrument. Optical rotations were determined on a Perkin-Elmer 241 polarimeter at ambient temperature. Flash column chromatography was performed with Kieselgel 60 (230–400 mesh ASTM). Medium-pressure liquid chromatography (MPLC) was done on prepacked EM lobar LiChroprep Si 60 columns. The Waters Prep 500 system refers to semipreparative HPLC with a 25-mm steel column packed with Kieselgel 60 (230–400 mesh). Thin-layer chromatography was performed on Merck silica gel 60 precoated plastic plates.

($CDCl_3$) δ 9.6 (q), 24.0 (q), 28.1 (t), 37.5 (t), 42.4 (t), 64.7 (t), 64.8 (t), 81.8 (d), 108.8 (s), 155.4 (s); IR (thin film) 2967, 2936, 2882, 1381, 1350, 1216, 1137, 1093, 1045, 874 cm^{-1}; $[\alpha]^{25}_D$ +89° (c = 1.6, $CHCl_3$); MS m/z 184 (M − 15), 87; high-resolution MS calcd for $C_9H_{14}NO_3$ 184.0974, found 184.0973.

(*R*)-4-Hydroxy-1-(2-methyl-1,3-dioxolan-2-yl)-2-hexanone (6).[16] To a solution of isoxazoline **12** (15 mg, 0.075 mmol), boric acid (9.5 mg, 0.154 mmol), and methanol/water (15:1, 2 mL) was added a catalytic amount of Ra-Ni. The system was evacuated and purged five times with H_2 using a 3-way stopcock with a H_2 balloon. The mixture was then stirred vigorously under H_2 at 25 °C for 90 min. CH_2Cl_2 (20 mL) was added, and the solution was then dried over $MgSO_4$. The mixture was concentrated under reduced pressure, and the residue was purified by chromatography (35:65 EtOAc/hexane). Removal of the solvent under reduced pressure yielded **6** (12 mg, 80%): ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.5 Hz), 1.41 (3 H, s), 1.41–1.57 (2 H, m), 2.60 (1 H, dd, J = 17.8, 9.0 Hz), 2.73 (1 H, dd, J = 17.8, 2.8), 2.79 (2 H, s), 3.05 (1 H, d, J = 3.3 Hz), 3.98 (5 H, m); IR (thin film) 3501 (br), 2967, 2935, 2925, 2883, 1710, 1379, 1120, 1054, 1040 cm^{-1}; $[\alpha]^{25}_D$ −54° (c 1.2, $CHCl_3$); MS m/z 187 (M − 15), 87, 59, 43; high-resolution MS calcd for $C_9H_{15}O_4$ 187.0970, found 187.0970.

(2*R*)-2,3-Dihydro-2-ethyl-6-methyl-4*H*-pyran-4-one (5). To a solution of β-hydroxy ketone **6** (11 mg, 0.054 mmol) and ether (5 mL) was added aqueous 3 N HCl (8 drops). After 20 h at 25 °C, the reaction mixture was dried over $MgSO_4$. The solvent was removed under reduced pressure at 20 °C, and the residue was purified by chromatography (97:3 CH_2Cl_2/Et_2O). Removal of the solvent under reduced pressure at 20 °C yielded (+)-hepialone (6.7 mg, 88%): ^1H NMR ($CDCl_3$) δ 1.02 (3 H, t, J = 7.4 Hz), 1.65–1.95 (2 H, m), 2.00 (3 H, s), 2.31–2.47 (2 H, m), 4.29 (1 H, m), 5.31 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 9.3 (q), 21.1 (q), 27.6 (t), 40.4 (t), 80.5 (d), 104.8 (d), 174.5 (s), 193.2 (s); IR (thin film) 3156, 2979, 1658, 1652, 1608, 1469, 1403, 1384, 1340, 1096, 909 cm^{-1}; $[\alpha]^{25}_D$ +212° (c 0.67, EtOH); MS m/z 140 (M^+), 85, 69, 56; high-resolution MS calcd for $C_8H_{12}O_2$ 140.0837, found 140.0838.

Ethyl 2-Methyl-1,3-dioxolane-2-butanoate. A solution of ethyl 4-oxohexanoate (31.64 g, 200 mmol), ethylene glycol (11.7 mL, 210 mmol), p-TSA·H_2O (190 mg, 1 mmol), and benzene (200 mL) was refluxed under Dean–Stark conditions for 16 h. The reaction mixture was concentrated under reduced pressure and distilled to give a clear oil (37.0 g, 92%), bp 95–105 °C (1.6–2.0 mmHg): ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7.1 Hz), 1.32 (3 H, s), 1.70 (4 H, m), 2.33 (2 H, t, J = 7.0 Hz), 3.94 (4 H, m), 4.13 (2 H, q, J = 7.1 Hz); IR (thin film) 2983, 2941, 2882, 1738, 1733, 1377, 1258, 1181, 1133, 1107, 1065 cm^{-1}; MS m/z 187 (M − 15), 157, 99, 87, 55; high-resolution MS calcd for $C_9H_{15}O_4$ 187.0970, found 187.0970.

2-Methyl-1,3-dioxolane-2-butanol. To a suspension of $LiAlH_4$ (3.79 g, 100 mmol) and ether (300 mL) at 0 °C was added the above ester (20.2 g, 100 mmol) dropwise. After 1 h at 25 °C, the slurry was quenched very slowly at 0 °C with H_2O (3.8 mL). Aqueous NaOH (15%, 3.8 mL) was then added followed by H_2O (11 mL). After 15 min at 25 °C, the reaction mixture was filtered. The filtrate was dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford a thick oil (15.8 g, 99%): ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.48 (2 H, m), 1.57 (2 H, m), 1.68 (2 H, m), 2.19 (1 H, s), 3.63 (2 H, t, J = 6.1 Hz), 3.94 (4 H, m); IR (thin film) 3412 (br), 2944, 2877, 1378, 1222, 1140, 1070, 1044, 856 cm^{-1}; MS m/z 145 (M − 15), 87, 55; high-resolution MS calcd for $C_7H_{13}O_3$ 145.0865, found 145.0865.

2-Methyl-1,3-dioxolane-2-butanal (16). To a solution of PCC (28.25 g, 131 mmol), NaOAc (2.15 g, 26.2 mmol), and CH_2Cl_2 (115 mL) was added the above alcohol (14.0 g, 87.4 mmol). After 3.5 h at 25 °C, ether (500 mL) was added. The reaction mixture was passed through Florisil, and the black residue was washed with ether (2 × 100 mL). The filtrates were concentrated under reduced pressure, and the residue was purified by chromatography using Waters Prep 500 (20:80 EtOAc/hexane). The solvent was removed under reduced pressure to give an oil (9.50 g, 69%): ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.70 (4 H, m), 2.47 (2 H, dt, J = 7.1, 1.5 Hz), 3.93 (4 H, m), 9.77 (1 H, t, J = 1.5 Hz); IR (thin film) 2983, 2958, 2884, 1734, 1378, 1253, 1218, 1175, 1139, 1064 cm^{-1}; MS m/z 143 (M − 15), 113, 99, 87, 55, 43; high-resolution MS calcd for $C_7H_{11}O_3$ 143.0708, found 143.0708.

2-Methyl-1,3-dioxolane-2-butanal Oxime (17). To a solution of aldehyde **16** (8.00 g, 50.6 mmol) and H_2O (100 mL) at 0 °C was added Na_2CO_3 (8.05 g, 75.9 mmol) followed by NH_2OH·HCl (5.28 g, 75.9 mmol) in H_2O (20 mL). After 7 h at 25 °C, the reaction mixture was extracted with ethyl acetate (3 × 150 mL). The extracts were dried over $MgSO_4$, and the residue was concentrated under reduced pressure. Purification by chromatography using Waters Prep 500 (30:70 EtOAc/hexane) and removal of the solvent under reduced pressure afforded the colorless oxime **17** (6.99 g, 80%): ^1H NMR ($CDCl_3$) 1:1 ratio of isomers δ 1.32 (3 H, s), 1.38 (3 H, s), 1.5–1.8 (8 H, m), 2.22 (2 H, q, J = 6.5 Hz, 2.40 (2 H, q, J = 5.7 Hz), 3.94 (8 H, m), 6.72 (1 H, t, J = 5.4 Hz), 7.42 (1 H, t, J = 6.1 Hz), 8.65 (1 H, s), 9.06 (1 H, s); IR (thin film) 3378, 3372, 2951, 2884, 1378, 1220, 1059, 949, 933, 858 cm^{-1}; MS m/z 158 (M − 15), 99, 87, 55; high-resolution MS calcd for $C_7H_{12}NO_3$ 158.0817, found 158.0817.

***N*-Hydroxy-2-methyl-1,3-dioxolane-2-butanimidoyl Chloride (18a).** To a solution of oxime **17** (3.36 g, 19.4 mmol) and DMF (50 mL) at 5 °C and under N_2 was added NCS (2.85 g, 21.3 mmol). After 8 h at 25 °C, the reaction mixture was poured into EtOAc (75 mL). The solution was washed with a 50:50 mixture of saturated aqueous NaCl solution/H_2O (2 × 150 mL) and H_2O (2 × 150 mL) and then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **18a** as a pale yellow oil (3.89 g, 96%): ^1H NMR ($CDCl_3$) δ 1.34 (3 H, s), 1.68–1.78 (4 H, m), 2.53 (2 H, t, J = 6.7 Hz), 3.96 (4 H, m), 8.66 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 20.8 (q), 23.8 (t), 36.6 (t), 37.7 (t), 64.7 (t), 64.8 (t), 110.0 (s), 141.1 (s); IR (thin film) 3323, 3320, 3313, 2983, 2962, 2888, 1737, 1380, 1150, 1098, 1063, 1044, 960 cm^{-1}; MS m/z 192 (M − 15), 156, 99, 87, 69, 55; high-resolution MS calcd for $C_7H_{11}NO_3{}^{35}Cl$ 192.0427, found 192.0427.

[3a*R*-[1(*S)-3aα,6α,7aβ]]-1-[[4,5-Dihydro-3-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-5-isoxazolyl]carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (19a).** To a solution of *N*-acryloyl camphor sultam **2** (1.40 g, 5.2 mmol), hydroximic chloride **18a**, (1.73 g, 8.3 mmol), and ether (270 mL) under N_2 was added Et_3N (1.16 mL, 8.3 mmole). After 14 h at 25 °C, the reaction mixture was filtered and then passed through 2 in. of silica gel. The solvent was removed under reduced pressure, and the residue was purified by chromatography using MPLC-Lobar C (40:20:40 Et_2O/CH_2Cl_2/hexane). Removal of the solvent under reduced pressure gave the major diastereomer **19a** (2.02 g, 89%): ^1H NMR ($CDCl_3$) δ 0.98 (3 H, s), 1.18 (3 H, s), 1.31 (3 H, s), 1.39 (2 H, m), 1.69 (4 H, m), 1.92 (3 H, m), 2.13 (2 H, m), 2.38 (2 H, m), 3.21 (1 H, dd, J = 17.2, 10.7 Hz), 3.32 (1 H, dd, J = 17.2, 6.9 Hz), 3.45 (1 H, d, J = 13.8 Hz), 3.55 (1 H, d, J = 13.8 Hz), 3.93 (5 H, m), 5.48 (1 H, dd, J = 10.5, 6.9 Hz); IR (thin film) 2959, 2884, 1699, 1377, 1334, 1272, 1239, 1223, 1167, 1136, 1121, 1064, 864, 767 cm^{-1}; $[\alpha]^{25}_D$ +176° (c 7.0, $CHCl_3$); MS m/z 440 (M^+), 198, 154, 87; high-resolution MS calcd for $C_{21}H_{32}N_2O_6S$ 440.1981, found 440.1983.

(*S*)-4,5-Dihydro-3-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-5-isoxazolemethanol. To a solution of isoxazoline **19a** (1.66 g, 3.77 mmol) and THF (200 mL) under N_2 was added a 1 M solution of L-Selectride in THF (9.4 mL, 9.42 mmol) over 30 s. After 45 min at 25 °C, the reaction mixture was quenched slowly with H_2O (2.4 mL). Addition of aqueous NaOH (15%, 2.4 mL) was followed by addition of 30% H_2O_2 (2.4 mL). The solution was diluted with EtOAc (300 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (80:20 EtOAc/hexane), and removal of the solvent under reduced pressure afforded a thick oil (742 mg, 86%): ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.69 (4 H, m), 1.89 (1 H, dd, J = 7.6, 6.0 Hz), 2.37 (2 H, m), 2.83 (1 H, dd, J = 17.0, 7.3 Hz), 2.9 (1 H, dd, J = 17.0, 10.7 Hz), 3.56 (1 H, m), 3.77 (1 H, m), 3.94 (4 H, m), 4.67 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 20.8 (t), 23.8 (q), 27.7 (t), 38.4 (t), 38.8 (t), 63.7 (t), 64.7 (t), 64.8 (t), 79.9 (d), 109.7 (s), 159.3 (s); IR (thin film) 3422 (br), 2954, 2879, 1378, 1219, 1062, 1050, 866 cm^{-1}; $[\alpha]^{25}_D$ +85° (c 3.5, $CHCl_3$); MS m/z 229 (M^+), 214, 198, 168, 154, 138, 128, 99, 87, 59, 55, 43; high-resolution MS calcd for $C_{11}H_{19}NO_4$ 229.1314, found 229.1315.

(*S*)-4,5-Dihydro-3-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-5-isoxazolemethanol 4-Methylbenzenesulfonate (20). To a solution of the above alcohol (770 mg, 3.36 mmol), p-toluenesulfonyl chloride (896 mg, 4.70 mmol), and CH_2Cl_2 (50 mL) was added Et_3N (0.70 mL, 5.03 mmol) followed by DMAP (41

mg, 0.34 mmol). After 9 h at 25 °C, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ether (200 mL) and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (45:55 EtOAc/hexane). The solvent was removed under reduced pressure to give the tosylate **20** (1.06 g, 83%): ^{1}H NMR ($CDCl_3$) δ 1.31 (3 H, s), 1.66 (4 H, m), 2.34 (2 H, m), 2.46 (3 H, s), 2.84 (1 H, dd, J = 17.3, 6.5 Hz), 3.05 (1 H, dd, J = 17.3, 10.7 Hz), 3.94 (4 H, m), 3.98 (1 H, dd, J = 10.5, 5.4 Hz), 4.06 (1 H, dd, J = 10.5, 4.8 Hz), 4.72 (1 H, m), 7.36 (2 H, d, J = 8.3 Hz), 7.79 (2 H, d, J = 8.3 Hz); MS m/z 383 (M^+), 368, 322, 282, 198, 154, 138, 131, 109, 99, 91, 87, 84, 59; high-resolution MS calcd for $C_{18}H_{25}NO_6S$ 383.1403, found 383.1403.

(*S*)-4,5-Dihydro-5-(iodomethyl)-3-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]isoxazole (21). A mixture of tosylate **20** (1.02 g, 2.66 mmol), NaI (1.99 g, 13.3 mmol), $NaHCO_3$ (90 mg), and methyl ethyl ketone (100 mL) was refluxed for 15 h. The reaction mixture was concentrated under reduced pressure and partitioned between ether (100 mL) and 5% sodium thiosulfate solution (100 mL). The organic phase was washed with H_2O (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure in the dark to afford **21** as a pale yellow oil (885 mg, 98%): ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.69 (4 H, m), 2.37 (2 H, m), 2.80 (1 H, dd, J = 17.4, 6.4 Hz), 3.13 (2 H, m), 3.33 (1 H, dd, J = 10.0, 4.0 Hz), 3.94 (4 H, m), 4.71 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 8.1 (t), 20.7 (q), 23.8 (t), 27.6 (t), 38.4 (t), 43.1 (t), 64.6 (t), 64.7 (t), 79.0 (d), 109.6 (s), 158.0 (s); IR (thin film) 2979, 2954, 2880, 1431, 1377, 1253, 1220, 1217, 1215, 1173, 1136, 1124, 1121, 1101, 1061, 1047, 882, 864 cm^{-1}; $[\alpha]^{25}_D$ +32.3° (*c* 16, $CHCl_3$); MS m/z 339 (M^+), 324, 296, 278, 238, 109, 99, 87, 59; high-resolution MS calcd for $C_{18}H_{18}NO_3I$ 339.0331, found 339.0331.

General Procedure for (*R*)-4,5-Dihydro-5-methyl-3-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]isoxazole (22). See Table I. To a solution of iodide **21** (1.0 equiv), Bu_3SnH (1.5 equiv), and indicated amount of solvent in an NMR tube was added a catalytic amount of AIBN. The tube was sealed and heated at the indicated temperature for 2 h. DBU (1.5 equiv) was then added at 25 °C. After 5 min, ether (2 mL) was added. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (30:70 EtOAc/hexane), and removal of the solvent under reduced pressure afforded the partially racemized product **22** in the indicated yield: ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.33 (3 H, d, J = 6.1 Hz), 1.68 (4 H, m), 2.36 (2 H, m), 2.51 (1 H, dd, J = 16.7, 7.8 Hz), 3.01 (1 H, dd, J = 16.7, 9.9 Hz), 3.94 (4 H, m), 4.68 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 20.9 (q), 21.0 (q), 23.9 (t), 27.9 (t), 38.5 (t), 43.7 (t), 64.7 (t), 64.8 (t), 76.1 (d), 109.7 (s), 158.7 (s); IR (thin film) 2978, 2955, 2931, 2881, 1456, 1435, 1378, 1307, 1253, 1220, 1133, 1108, 1060, 866 cm^{-1}; $[\alpha]^{25}_D$ see Table I; MS m/z 231 (M^+), 198, 99, 87, 69, 57, 55, 43; high-resolution MS calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1365.

(*R*)-6-Hydroxy-1-(2-methyl-1,3-dioxolan-2-yl)-4-heptanone (23). To a solution of iodide **21** (357 mg, 1.05 mmol), boric acid (134 mg, 2.16 mmol), and methanol/water (15:1) (30 mL) was added excess Ra-Ni. The system was evacuated and purged five times with H_2 using a 3-way stopcock fitted with a H_2 balloon. The mixture was then stirred vigorously under H_2 at 25 °C for 16 h. CH_2Cl_2 (80 mL) was added, and the solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (50:50 EtOAc/hexane). Removal of the solvent under reduced pressure yielded **23** (168 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 1.19 (3 H, d, J = 6.3 Hz), 1.31 (3 H, s), 1.60–1.73 (4 H, m), 2.46 (2 H, t, J = 7.2 Hz), 2.50 (1 H, dd, J = 17.5, 8.5 Hz), 2.60 (1 H, dd, J = 17.5, 3.5 Hz), 3.21 (1 H, d, J = 2.0 Hz), 3.93 (4 H, m), 4.21 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 18.0 (q), 22.4 (q), 23.7 (t), 38.2 (t), 43.3 (t), 50.5 (t), 63.9 (d), 64.6 (t), 64.7 (t), 109.8 (s), 211.9 (s); IR (thin film) 3457 (br), 2967, 2933, 2886, 1709, 1377, 1254, 1220, 1129, 1116, 1068, 1066, 1043, 947 cm^{-1}; $[\alpha]^{25}_D$ −45.5° (*c* 1.6, $CHCl_3$); MS m/z 201 (M − 15), 157, 99, 87, 55; high-resolution MS calcd for $C_{10}H_{17}O_4$ 201.1127, found 201.1127.

[*R*-(*R,*S**)]-7-(2-Methyl-1,3-dioxolan-2-yl)-2,4-heptanediol (14).**[26] To a solution of β-hydroxy ketone **23** (82 mg, 0.379 mmol) and THF/MeOH (4:1) (5 mL) at −70 °C and under N_2 was added dropwise a 1 M solution of diethylmethoxyborane in THF (398 mL, 0.398 mmol). After 15 min, $NaBH_4$ (16 mg, 0.417 mmol) was added. After 4 h, the reaction mixture was quenched with H_2O (4 drops). Aqueous NaOH (15%, 4 drops) was added followed by 30% H_2O_2 (4 drops). The reaction mixture was diluted with EtOAc (20 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. Purification of the residue by chromatography (70:30 EtOAc/hexane) and removal of the solvent under reduced pressure afforded exclusively the *syn*-1,3-diol **14** (71 mg, 86%): ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, d, J = 6.2 Hz), 1.32 (3 H, s), 1.38–1.59 (6 H, m), 1.60–1.70 (2 H, m), 3.47 (1 H, d, J = 3.2 Hz), 3.54 (1 H, d, J = 2.6 Hz), 3.85 (1 H, m), 3.94 (4 H, m), 4.04 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 19.7 (t), 23.7 (q), 24.0 (q), 38.1 (t), 38.9 (t), 44.4 (t), 64.5 (t), 64.6 (d), 68.8 (d), 72.5 (d), 110.0 (s); IR (thin film) 3402 (br), 2963, 2936, 1378, 1315, 1251, 1221, 1138, 1122, 1056, 948, 862, 835 cm^{-1}; $[\alpha]^{25}_D$ −7.0° (*c* 7.0, $CHCl_3$); MS m/z 203 (M − 15), 159, 141, 87, 71, 59, 43; high-resolution MS calcd for $C_{10}H_{19}O_4$ 203.1283, found 203.1283.

(1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (13). A solution of diol **14** (62 mg, 0.284 mmol) and ether (10 mL) was treated with aqueous 3 N HCl (24 drops). After 16 h at 25 °C, the reaction mixture was dried over $MgSO_4$ and concentrated under reduced pressure at 15 °C. The residue was purified by chromatography (95:5 pentane/ether), and removal of the solvent under reduced pressure at 15 °C yielded (1*R*,3*R*,5*S*)-**13** (25 mg, 57%): ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, d, J = 6.1 Hz), 1.27 (3 H, s), 1.20–1.82 (6 H, m), 2.00–2.20 (2 H, m), 3.94 (1 H, m), 4.27 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.3 (t), 20.9 (q), 27.4 (q), 2.97 (t), 34.9 (t), 36.9 (t), 61.5 (d), 66.9 (d), 97.5 (s); IR (thin film) 2938, 1376, 1238, 1223, 1201, 1195, 1161, 1150, 1130, 1079, 1068, 1030, 967, 942, 874 cm^{-1}; $[\alpha]^{25}_D$ −46.2° (*c* 2.2, pentane); MS m/z 156 (M^+), 128, 114, 105, 87, 81, 71, 68, 58, 55, 43; high-resolution MS calcd for $C_9H_{16}O_2$ 156.1150, found 156.1150.

2-(2-Nitroethyl)-1,3-dioxolane (30). A solution of bromo acetal **29** (16.56 g, 91.5 mmol), $NaNO_2$ (12.6 g, 183 mmol), and DMF (125 mL) was stirred at 25 °C for 48 h. The reaction mixture was then poured into H_2O (500 mL) and extracted with ether (4 × 150 mL). The extracts were washed with H_2O (5 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (13:87 EtOAc/hexane). Removal of the solvent under reduced pressure afforded **30** as a clear oil (2.40 g, 18%): ^{1}H NMR ($CDCl_3$) δ 2.41 (2 H, dt, J = 6.9, 3.6 Hz), 3.91 (4 H, m), 4.48 (2 H, t, J = 7.0 Hz), 5.01 (1 H, t, J = 3.7 Hz). *Caution*: on one occasion a violent explosion occurred while attempting to purify this compound by distillation rather than chromatography.

[3a*R*-[1(*S),3aα,6aα,7aβ]]-1-[[4,5-Dihydro-3-(1,3-dioxolan-2-ylmethyl)-5-isoxazolyl]carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (31a).** To a solution of *N*-acryloyl camphor sultam **2** (2.10 g, 7.8 mmol), nitro acetal **30** (2.29 g, 15.6 mmol), and benzene (200 mL) at 25 °C and under N_2 was added PhNCO (2.54 mL, 23.4 mmol) followed by Et_3N (2.17 mL, 15.6 mmol). After 24 h, PhNCO (2.54 mL, 23.4 mmol) and Et_3N (2.17 g, 15.6 mmol) were added. After an additional 24 h, the reaction mixture was diluted with EtOAc (250 mL) and filtered. The filtrate was passed through 2 in. of silica gel, and the silica was flushed with EtOAc. The solvent was removed under reduced pressure, and the residue was purified by MPLC-Lobar C (40:60 EtOAc/hexane). After removal of the solvent under reduced pressure, the major diastereomer was isolated by chromatography (40:20:40 Et_2O/CH_2Cl_2/hexane). Removal of the solvent under reduced pressure afforded **31** as a thick gum (2.15 g, 70%): ^{1}H NMR ($CDCl_3$) δ 0.98 (3 H, s), 1.18 (3 H, s), 1.40 (2 H, m), 1.90 (3 H, m), 2.12 (2 H, m), 2.76 (2 H, m), 3.37 (2 H, m), 3.45 (1 H, d, J = 13.8 Hz), 3.55 (1 H, d, J = 13.8 Hz), 3.85–4.05 (5 H, m), 5.07 (1 H, t, J = 4.5 Hz), 5.50 (1 H, dd, J = 10.8, 7.2 Hz); IR (thin film) 2961, 2888, 1700, 1395, 1333, 1273, 1240, 1223, 1167, 1136, 1036, 754 cm^{-1}; $[\alpha]^{25}_D$ +209° (*c* 4, $CHCl_3$); MS m/z 398 (M^+), 156, 112, 73; high-resolution MS calcd for $C_{18}H_{26}N_2O_6S$ 398.1512, found 398.1512.

(*S*)-3-(1,3-Dioxolan-2-ylmethyl)-4,5-dihydro-α,α-dimethyl-5-isoxazolemethanol (32). To a solution of isoxazoline **31a** (1.53 g, 3.84 mmol) and THF (150 mL) at −78 °C under N_2 was added a 2.6 M solution of methylmagnesium bromide in ether (3.25 mL, 8.45 mmol). After stirring 45 min at −78 °C and then 90 min at 25 °C, the reaction mixture was quenched with H_2O (2 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography

(50:50 EtOAc/hexane). Removal of the solvent under reduced pressure afforded **32** as a thick oil (0.592 g, 72%): ^{1}H NMR ($CDCl_3$) δ 1.14 (3 H, s), 1.29 (3 H, s), 1.96 (1 H, s), 2.72 (2 H, d, J = 4.7 Hz), 2.99 (2 H, m), 3.95 (4 H, m), 4.39 (1 H, dd, J = 10.5, 9.0 Hz), 5.06 (1 H, t, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$) δ 24.4, 26.2, 32.6, 38.4, 65.0, 65.1, 71.1, 86.7, 101.8, 155.5; IR (thin film) 3440 (br), 2973, 2890, 1470, 1364, 1341, 1231, 1134, 1024, 945, 887, 826 cm^{-1}; $[\alpha]^{25}_D$ +114° (c 1.5, $CHCl_3$); MS m/z 215 (M^+), 200, 156, 126, 112, 84, 73, 59, 49; high-resolution MS calcd for $C_{10}H_{17}NO_4$ 215.1158, found 215.1157.

5-Amino-6-(1,3-dioxolan-2-yl)-2-methyl-2,3-hexanediol (28). To a suspension of $LiAlH_4$ (328 mg, 8.64 mmol) and ether (100 mL) at −78 °C and under N_2 was added dropwise a solution of alcohol **32** (310 mg, 1.44 mmol) and ether (6 mL). After 20 h at 25 °C, the reaction mixture was slowly quenched with H_2O (300 μL), aqueous NaOH (15%, 300 μL), and H_2O (900 μL). The mixture was dried over $MgSO_4$, and the solvent was removed under reduced pressure, yielding **28** as a clear oil (305 mg, 97%): ^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 2.9 Hz), 1.10 (3 H, s), 1.15–1.90 (7 H, m), 3.08 (1 H, m), 3.37–3.65 (2 H, m), 3.70–3.96 (4 H, m), 4.87 (1 H, m); IR (thin film) 3359 (br), 2971, 2888, 1582, 1472, 1383, 1223, 1138, 1088, 1032, 961, 853, 818 cm^{-1}; $[\alpha]^{25}_D$ −3.2° (c 3.7, $CHCl_3$); MS m/z 160 (M − 59), 132, 116, 73, 59, 44; high-resolution MS calcd for $C_7H_{14}NO_3$ 160.0974, found 160.0974.

(*S*)-6-(1,3-Dioxolan-2-yl)-2-methyl-2,3-hexanediol (27).[32] To a solution of amino alcohol **28** (218 mg, 0.99 mmol) and CH_2Cl_2 (4 mL) at 0 °C was added 2.5 M aqueous NaOH (2 mL) followed by hydroxylamine-*O*-sulfonic acid (281 mg, 2.48 mmol). After 15 min, 2.5 M aqueous NaOH (2 mL) and hydroxylamine-*O*-sulfonic acid (281 mg, 2.48 mmol) were added. After 1 h at 25 °C, 1 g of NaCl was added. The reaction mixture was extracted with EtOAc (4 × 25 mL). The extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by chromatography (75:25 EtOAc/hexane), and removal of the solvent under reduced pressure affored **27** as a clear oil (110 mg, 54%): ^{1}H NMR ($CDCl_3$) δ 1.14 (3 H, s), 1.19 (3 H, s), 1.21–1.51 (3 H, m), 1.71 (3 H, m), 2.12 (1 H, s), 2.43 (1 H, d, J = 3.1 Hz), 3.36 (1 H, d, J = 9.9 Hz), 3.82–3.99 (4 H, m), 4.86 (1 H, t, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.2 (q), 23.3 (q), 26.5 (t), 31.4 (t) 33.6 (t), 64.9 (t), 65.0 (t), 73.1 (s), 78.4 (d), 104.6 (d); IR (thin film) 3441 (br), 2953, 2878, 1661, 1462, 1408, 1381, 1140, 1084, 1044, 959 cm^{-1}; $[\alpha]^{25}_D$ −23° (c 1.2, $CHCl_3$); MS m/z 145 (M − 59), 127, 99, 84, 73, 67, 59, 55, 43; high-resolution MS calcd for $C_7H_{13}O_3$ 145.0865, found 145.0865.

(*S*,*S*)-7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (26). To a solution of diol **27** (110 mg, 0.49 mmol) and benzene (2 mL) was added *p*-TSA·H_2O (10 mg). After 48 h at 60 °C, the reaction mixture was concentrated under reduced pressure at 20 °C. The residue was purified by chromatography (94:6 pentane/ether), and removal of the solvent under reduced pressure below 20 °C yielded (−)-**26** (42 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 1.27 (3 H, s), 1.43 (3 H, s), 1.5–1.7 (4 H, m), 1.8–2.1 (2 H, m), 3.83 (1 H, s), 5.51 (1 H, s); ^{1}H NMR (CCl_4) δ 1.19 (3 H, s), 1.36 (3 H, s), 1.42–1.70 (4 H, m), 1.71–2.04 (2 H, m), 3.69 (1 H, s), 5.33 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 15.7 (t), 20.6 (q), 25.1 (t), 29.0 (q), 30.3 (t), 79.5 (d), 80.5 (s), 102.0 (d); IR (CCl_4) 2950, 1719, 1549, 1364, 1246, 1217, 1179, 1130, 1113, 1063, 1028, 1007, 984 cm^{-1}; $[\alpha]^{28}_D$ −95.2° (c 2.3, $CHCl_3$); $[\alpha]^{22}_D$ −92.0° (c 2.0, Et_2O); MS m/z 142 (M^+), 127, 96, 84, 71, 55; high-resolution MS calcd for $C_8H_{14}O_2$ 142.1994, found 142.1994.

[3a*R*-(3aα,6α,7aβ)]-Hexahydro-8,8-dimethyl-1-(2-methyl-1-oxo-2-propenyl)-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (33). To a suspension of dry, oil-free NaH (0.67 g, 27.9 mmol) and toluene (120 mL) was added L-2,10-camphorsultam (4.00 g, 18.6 mmol). After 1 h at 25 °C, methacryloyl chloride (4.0 mL, 37.2 mmol) was added dropwise. After 1 h, the reaction mixture was concentrated under reduced pressure and diluted with ether (200 mL). The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography using Waters Prep 500 (13:87 EtOAc/hexane). The solvent was removed under reduced pressure to yield pure **33** (5.07 g, 96%): ^{1}H NMR ($CDCl_3$) δ 0.99 (3 H, s), 1.23 (3 H, s), 1.39 (2 H, m), 1.57 (1 H, m), 1.96 (4 H, m), 1.98 (3 H, s), 3.39 (1 H, d, J = 13.7 Hz), 3.51 (1 H, d, J = 13.7 Hz), 4.03 (1 H, dd, J = 7.3, 5.0 Hz), 5.67 (1 H, d, J = 11.2 Hz), 5.67 (1 H, d, J = 9.8 Hz); IR (thin film) 2961, 1667, 1632, 1331, 1196, 1165, 1132, 1115, 1067, 980 cm^{-1}; $[\alpha]^{22}_D$ +93° (c 1, $CHCl_3$).

[3a*R*-[1(*R and *S**),3aα,6α,7aβ]]-1-[[4,5-Dihydro-5-methyl-3-[(2-methyl-1,3-dioxolan-2-yl)methyl]-5-isoxazolyl]carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (34a and 34b).** To a solution of *N*-methacryloyl camphor sultam **33** (1.30 g, 4.59 mmol), nitro ketal **30** (1.49 g, 9.17 mmol), and benzene (40 mL) under N_2 at 50 °C was added PhNCO (1.5 mL, 13.8 mmol) followed by Et_3N (1.3 mL, 9.17 mmol). After 48 h, PhNCO (1.5 mL, 13.8 mmol) and Et_3N (1.3 mL, 9.17 mmol) were added. After 24 h at 80 °C, the reaction mixture was filtered, and the filtrate was poured into H_2O (100 mL). The mixture was extracted into ether (2 × 200 mL). The extracts were washed with H_2O (2 × 200 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by chromatography (40:60 EtOAc/hexane). Removal of the solvent under reduced pressure afforded the major cycloadduct **34a** (1.10 g, 56%), stereochemistry unassigned: ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, s), 1.19 (3 H, s), 1.33 (2 H, m), 1.34 (3 H, s), 1.64 (3 H, s), 1.80–2.00 (4 H, m), 2.06 (1 H, m), 2.69 (2 H, s), 2.90 (1 H, d, J = 17.7 Hz), 3.43 (1 H,d, J = 13.6 Hz), 3.53 (1 H, d, J = 13.5 Hz), 3.67 (1 H, d, J = 17.8 Hz), 3.94 (4 H, m), 4.00 (1 H, m).

[3a*R*-[1(*E*),3aα,6α,7aβ]]-Hexahydro-8,8-dimethyl-1-(1-oxo-2-butenyl)-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (36). To a suspension of dry, oil-free NaH (84 mg, 3.48 mmol) and toluene (20 mL) was added L-2,10-camphor sultam (0.50 g, 2.32 mmol). After 1 h at 25° C, crotonyl chloride (494 μL, 4.64 mmol) was added dropwise. After 18 h, NaH (56 mg, 2.32 mmol) and crotonyl chloride (222 μL, 2.32 mmol) were added, and the reaction mixture was heated at 45 °C for 18 h. The suspension was then quenched with H_2O (8 drops), diluted with ether (50 mL), and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (20:80 EtOAc/hexane). Removal of the solvent under reduced pressure afforded **36** (361 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, s), 1.17 (3 H, s), 1.38 (2 H, m), 1.88 (3 H, m), 1.93 (3 H, dd, J = 6.9, 1.6 Hz), 2.12 (2 H, m), 3.44 (1 H, d, J = 13.8 Hz), 3.51 (1 H, d, J = 13.8 Hz), 3.93 (1 H, dd, J = 7.3, 5.4 Hz), 6.58 (1 H, dq, J = 14.9, 1.5 Hz), 7.10 (1 H, m).

Cycloadducts 37a, 37b, 38a, and 38b. To a solution of *N*-crotonyl sultam **36** (57 mg, 0.2 mmol), benzaldoxime chloride (62 mg, 0.4 mmol), and ether (20 mL) was added Et_3N (56 μL, 0.4 mmol). After 20 h at 34 °C, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (15:85 EtOAc/hexane), and the solvent was removed under reduced pressure to obtain **37a**, **37b**, and a mixutre of **38a** and **38b** (65 mg, 82% total).

[3a*R*-[1(4*R,5*R**),3aα,6α,7aβ]]-1-[(4,5-Dihydro-4-methyl-3-phenyl-5-isoxazolyl)carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (37a)**: colorless film (31 mg, 39%); ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, s), 1.19 (3 H, s), 1.25–1.55 (2 H, m), 1.42 (3 H, d, J = 7.2 Hz), 1.78–2.22 (5 H, m), 3.46 (1 H, d, J = 13.8 Hz), 3.56 (1 H, d, J = 13.8 Hz), 3.92 (1 H, dd, J = 7.7, 4.7 Hz), 4.09 (1 H, m), 5.32 (1 H, d, J = 3.2 Hz), 7.38 (3 H, m), 7.68 (2 H, m).

[3a*R*-[1(4*S,5*S**),3aα,6α,7aβ]]-1-[(4,5-Dihydro-4-methyl-3-phenyl-5-isoxazolyl)carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (37b)**: colorless film (3 mg, 4%); ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, s), 1.17 (3 H, s), 1.20–1.50 (2 H, m), 1.48 (3 H, d, J = 7.1 Hz, 1.80–2.20 (5 H, m), 3.50 (1 H, d, J = 13.9 Hz), 3.55 (1 H, d, J = 13.9 Hz), 3.73 (1 H, m), 3.94 (1 H, t, J = 6.3 Hz), 5.40 (1 H, d, J = 2.9 Hz), 7.41 (3 H, m), 7.68 (2 H, m).

[3a*R*-[1(4*R,5*S**),3aα,6α,7aβ]]-1-[(4,5-Dihydro-4-methyl-3-phenyl-5-isoxazolyl)carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (38a) and [3a*R*-[1(4*S**,5*R**),3aα,6α,7aβ]]-1-[(4,5-dihydro-4-methyl-3-phenyl-5-isoxazolyl)carbonyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (38b)**: colorless film (31 mg, 39%); **15a** ^{1}H NMR ($CDCl_3$) δ 4.86 (1 H, d, J = 4.8 Hz); **15b** ^{1}H NMR ($CDCl_3$) δ 4.56 (1 H, d, J = 4.8 Hz).

General Procedure for Competitive Rate Reactions. To a solution of olefin 1 (0.20 mmol), olefin 2 (0.20 mmol), phenyl hydroximic chloride (0.10 mmol), ether (20 mL), and hexane (20 mL), was added Et_3N (0.11 mmol). After 48 h at 25 °C, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was then analyzed by ^{1}H

NMR ($CDCl_3$) to determine the cycloadduct ratios.

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Supplementary Material Available: Crystallographic data for **33** and ^1H NMR and ^{13}C NMR spectra for **10a, 11, 12, 6, 5, 19a, 20, 23, 14, 13, 31a, 32, 28, 27, 26** (37 pages). Ordering information is given on any current masthead page.

Selenosulfonation of Conjugated Enynes and the Enyne Equivalent 1,4-Dichloro-2-butyne. Preparation of Sulfonyl-Substituted Allenic Alcohols and Dienes Using [2,3] Sigmatropic Rearrangements and Organocuprate Additions

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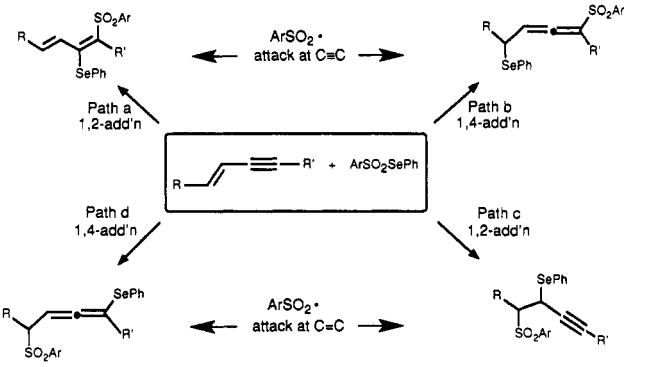
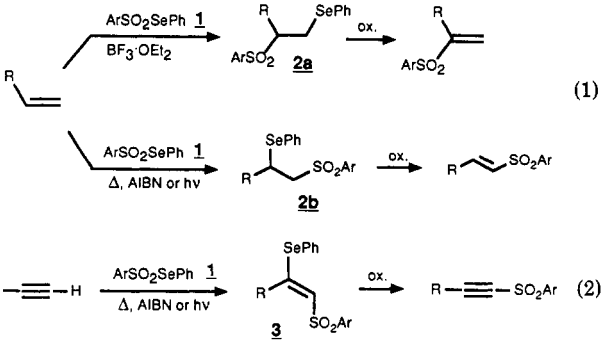
Conjugated enynes undergo free-radical selenosulfonation under either photochemical or thermal conditions with *Se*-phenyl *p*-tolueneselenosulfonate (**1**). Addition to the triple bond occurred preferentially with enynes having an acetylenic terminus (**6–8**) affording 1,2-adducts **10–12**, respectively, as well as the 1,4-adduct **13** from **8**. Enyne **9**, which has a terminal olefin and a disubstituted acetylene moiety, afforded 1,2- and 1,4-addition products to the double bond (**14** and **15**, respectively). [2,3] sigmatropic rearrangement of the selenoxides of the 1,2-adducts **10–12** produced the sulfonyl-substituted allenic alcohols **18–20**, respectively. The rearrangement was stereospecific, providing that excess oxidant was employed and the reaction promptly worked up. Otherwise, equilibration occurred and the products were obtained as mixtures of diastereomers. 1,4-Dichloro-2-butyne was converted to the sulfonyl-substituted allenic alcohol **23** by selenosulfonation, reductive dehalogenation, oxidation, and [2,3] sigmatropic rearrangement of the resulting selenoxide. The addition of organocuprates to **23**, followed by dehydration, afforded a series of 3-alkyl- or propenyl-substituted 2-sulfonyl-1,3-dienes **5a–e**. Alternatively, the treatment of **23** with acetic anhydride–triethylamine or thionyl chloride produced the 3-acetoxy- and 3-chloro-2-sulfonyl-1,3-dienes **5f** and **5g**, respectively. These methods therefore provide convenient access to a variety of synthetically useful sulfonyl-substituted allenic alcohols and dienes.

Unsaturated sulfones have numerous synthetic applications[1] that are stimulating interest in new methods for their preparation. The selenosulfonation reaction, where a selenosulfonate ($ArSO_2SePh$, **1**) undergoes electrophilic or free-radical addition to an unsaturated organic substrate, provides a convenient approach to this objective. In general, the resulting β-(phenylseleno)alkyl or β-(phenylseleno)vinyl sulfones (**2** and **3**, respectively) are subjected to selenoxide elimination, resulting in regeneration of the original unsaturated site, but with the newly appended sulfone group. The selenosulfonation of olefins[2] and acetylenes[3] thus provides convenient access to vinyl (eq 1) and acetylenic sulfones (eq 2), respectively. Variations of the latter process can be exploited for the preparation of allenic[4] and enamine[5] sulfones, while the selenosulfonation of allenes,[6] conjugated dienes,[2a,7] vinyl and acetylenic cyclopropanes,[8] and related compounds affords various other types of useful unsaturated sulfones. The selenosulfonates themselves are stable, crystalline, odorless solids that are easily handled and readily available.[9]

Scheme I





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