since a Baeyer–Villiger reaction can now be used to install the C4 oxygen. A serendipitous result provides a mechanism for the isomerization **12a** → **12b**. Thus treatment of **12a** with ethylene glycol and camphorsulfonic acid led not to a ketal but to a 3:2 mixture of the readily separated isomers **12b** and **12a**, respectively.

The work described herein outlines the second route[5f] to provide the trichothecane system in optically active form. The dense functionalization of **12a** and **12b** should permit the preparation of a wide array of trichothecanoid analogues.

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Arylation of Diethyl Phosphate by *N*-(Sulfonatooxy)acetanilides: A Model for a Possible in Vivo Reaction of Carcinogenic Metabolites of Aromatic Amides

Summary: *N*-(Sulfonatooxy)acetanilides, which serve as models for the carcinogenic metabolites of aromatic amides, arylate diethyl phosphate in aqueous solution.

Sir: Sulfuric acid esters of *N*-hydroxy-*N*-arylacetamides have been implicated as important carcinogenic metabolites of polycyclic *N*-arylacetamides.[1,2] Almost all the investigations concerned with the in vivo activity of these species have concentrated on their reactions with the purine and pyrimidine bases of DNA and RNA.[1,3] Although a number of alkylating and arylating agents have been shown to react with the phosphate backbone of DNA to form stable triesters or cause chain cleavage,[4] the possibility that the *N*-(sulfonatooxy)-*N*-arylacetamides may undergo a similar reaction has been given scant consideration.[5] Since such a reaction may be important to the in vivo activity of these reagents, we have investigated the reactions of the model compound *N*-(sulfonatooxy)-*p*-chloroacetanilide (**1**)[6] with diethyl phosphate in aqueous solution. Two ring-phosphorylated products, **2** and **3**, have been isolated from these reactions and characterized.

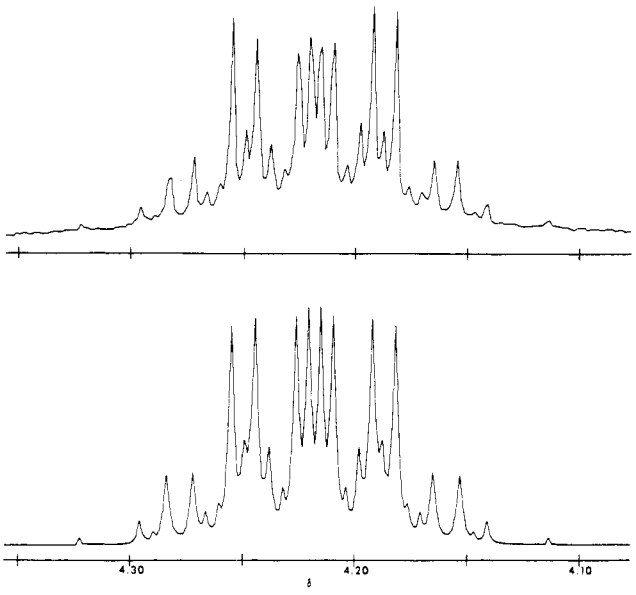

Figure 1. Observed (upper) and calculated (lower) ^{1}H NMR spectra for **2** in the methylene resonance region. Parameters used to generate the calculated spectrum are shown in Table I.

The decomposition of **1** (5×10^{-5} M) at 40 °C in 5% CH_3CN–H_2O containing 0.5 M diethyl phosphate at pH 3.1 follows a first-order pattern when monitored by UV spectroscopic methods.[7] The rate constant for the decomposition of **1** under these conditions is $(8.4 \pm 0.1) \times 10^{-2}$ h^{-1}, which is comparable to the rate constant for its decomposition under similar conditions in the absence of diethyl phosphate.[6] When the decomposition of **1** [$(1.25–2.50) \times 10^{-3}$ M] in the presence of diethyl phosphate is monitored by HPLC (μ-Bondapak C-18 reverse-phase column, 1/1 MeOH/H_2O solvent) two products, which are not observed in the absence of diethyl phosphate, can be detected. These materials can be separated from the other solvolysis products[6] by extraction into CH_2Cl_2, followed by preparative layer chromatography on silical gel (4/1 CH_2Cl_2/EtOAc eluent). The two compounds, which elute as a single band under these conditions, can then be separated from each other by preparative HPLC (Altex Ultrasphere-ODS 10 mm × 25 cm, 1/1 MeOH/H_2O solvent).

All spectral data obtained for these compounds indicate that they are ring-phosphorylated isomers.[8,9] The major

(1) Several recent reviews include: Miller, J. A. *Cancer Res.* **1970**, *30*, 559–576. Kriek, E. *Biochim. Biophys. Acta* **1974**, *355*, 177–203. Miller, E. C. *Cancer Res.* **1978**, *38*, 1479–1496. Miller, E. C.; Miller, J. A. *Cancer (Philadelphia)* **1981**, *47*, 2327–2345.

(2) DeBaun, J. R.; Miller, E. C.; Miller, J. A. *Cancer Res.* **1970**, *30*, 577–595. Weisburger, J. H.; Yamamoto, R. S.; Williams, G. M.; Grantham, P. H.; Matsushima, T.; Weisburger, E. K. *Ibid.* **1972**, *32*, 491–500. Kadlubar, F. F.; Miller, J. A.; Miller, E. C. *Ibid.* **1976**, *36*, 2350–2359. King, C. M.; Philipps, B. *J. Biol. Chem.* **1969**, 244, 6209–6216.

(3) Kriek, E.; Reitsema, J. *Chem.-Biol. Interact.* **1971**, *3*, 397–400. Scribner, J. D.; Naimy, N. K. *Cancer Res.* **1973**, 33, 1159–1164; **1975**, *35*, 1416–1421. Westra, J. G.; Kriek, E.; Hittenhausen, H. *Chem.-Biol. Interact.* **1976**, *15*, 149–164. Scribner, N. K.; Scribner, J. D.; Smith, D. L.; Schram, K. H.; McCloskey; J. A. *Ibid.* **1979**, *26*, 27–46. Saffhill, R.; Abbott, P. J. *Ibid.* **1983**, *44*, 95–110; Beland, F. A.; Dooley, K. L.; Jackson, C. D. *Cancer Res.* **1982**, *42*, 1348–1354. Kennelly, J. C.; Beland, F. A.; Kadlubar, F. F.; Martin, C. N. *Carcinogenesis* **1984**, *5*, 407–412 and references therein.

(4) Singer, B. *Prog. Nucleic Acid Res. Mol. Biol.* **1975**, *15*, 219–284 and references therein. Gamper, H. B.; Tung, A. S.-C.; Straub, K.; Bartholomew, J. C.; Calvin, M. *Science (Washington, D.C.)* **1977**, *197*, 671–674.

(5) We are aware of only one report that indicates that *N*-acetoxy-4-acetamidostilbene reacts with the phosphate backbone of RNA, although no triester derivatives were isolated: Scribner, N. K.; Scribner, J. D. *Chem.-Biol. Interact.* **1979**, *26*, 47–55. It is not clear whether strand breaks induced in RNA and DNA by derivatives of *N*-hydroxy-*N*-arylacetamides are caused by triester formation, depurination, or some other mechanism: Vaught, J. B.; Lee, M.-S.; Shayman, M. A.; Thissen, M. R., King, C. M. *Chem.-Biol. Interact.* **1981**, *34*, 109–124. Drinkwater, N. R.; Miller, E. C.; Miller, J. A. *Biochemistry* **1980**, *19*, 5087–5092; Kadlubar, F. F.; Melchior, W. B.; Flammang, T. J.; Springgate, C.; Moss, A. J.; Nagle, W. A. *J. Supramol. Struct. Cell. Biochem., Suppl.* **1981**, *5*, 457.

(6) Novak, M.; Pelecanou, M.; Roy, A. K.; Andronico, A. F.; Plourde, F. M.; Olefirowicz, T. M.; Curtin, T. J. *J. Am. Chem. Soc.* **1984**, *106*, 5623–5631.

(7) The diethyl phosphate was titrated with 1.0 N KOH to achieve a base/acid ratio of ca. 20/1.

(8) **2** was isolated as a white, waxy solid: mp 69.0–70.5 °C; IR (KBr) 3300, 3260, 2950, 1695, 1600, 1530, 1265, 1050 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.4 (1 H, s, br), 8.17 (1 H, d, J = 8.8 Hz), 7.23 (1 H, dd, J_{PH} = 1.35 Hz, J_{HH} = 2.25 Hz), 7.17 (1 H, m, J_{PH} = 1.0 Hz, J_{HH} = 2.25, 8.8 Hz), 4.23 (2 H, m, $^3J_{PH}$ = 8.55 Hz, $^3J_{HH}$ = 7.11 Hz, $^2J_{HH}$ = 10.09 Hz), 4.20 (2 H, m, $^3J_{PH}$ = 8.55 Hz, $^3J_{HH}$ = 7.11 Hz, $^2J_{HH}$ = 10.09 Hz), 2.15 (3 H, s), 1.34 (6 H, td, $^4J_{PH}$ = 1.10 Hz, $^3J_{HH}$ = 7.11 Hz); MS, *m/e* (relative intensity) 321 (M^+, 42.3), 323 ($M + 2^+$, 13.8), 281 (35.0), 279 (100), 253 (13.6), 251 (39.8), 225 (17.4), 223 (51.2); high-resolution MS, *m/e* 321.0532 ($C_{12}H_{17}NO_5P^{35}Cl$ requires 321.0534), 323.0484 ($C_{12}H_{17}NO_5P^{37}Cl$ requires 323.0504).

(9) **3** was isolated as a clear oil: IR (neat) 3270, 3000, 1690, 1600, 1530, 1270, 1030 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 8.28 (1 H, d, J_{HH} = 9.4 Hz), 7.5 (1 H, s, br), 7.30 (1 H, dd, J_{PH} = 1.1 Hz, J_{HH} = 2.8 Hz), 7.12 (1 H, m, J_{PH} = 0.9 Hz, J_{HH} = 2.8, 9.1 Hz), 4.19 (4 H, quintet, $J_{PH} \simeq J_{HH}$ = 7.1 Hz), 2.19 (3 H, s), 1.34 (6 H, td, J_{PH} = 1.0 Hz, J_{HH} = 7.1 Hz); MS, *m/e* (relative intensity) 321 (M^+, 51.2), 323 ($M + 2^+$, 18.5), 286 (76.3), 281 (34.6), 279 (100), 253 (12.9), 251 (45.4), 225 (19.5), 223 (56.9); high-resolution MS, *m/e* 321.0541 ($C_{12}H_{17}NO_5P^{35}Cl$ requires 321.0534), 323.0504 ($C_{12}H_{17}NO_5P^{37}Cl$ requires 323.0504).

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Table I. Calculated Chemical Shifts and Coupling Constants for 2[a]

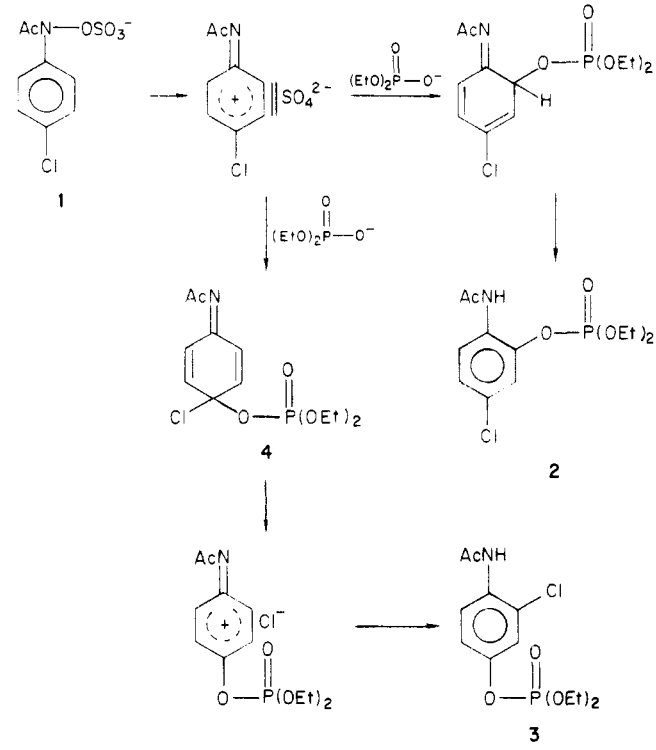
ν_{H_a}	1059.064 ± 0.030
ν_{H_b}	1051.247 ± 0.031
ν_{CH_3}	335.981 ± 0.018
$^2J_{H_aH_b}$	10.092 ± 0.031
$^3J_{POCH_a}$, $^3J_{POCH_b}$	8.545 ± 0.031[b]
$^3J_{H_aCCH_3}$, $^3J_{H_bCCH_3}$	7.110 ± 0.015[b]
$^4J_{POCCH_3}$	1.101 ± 0.036

[a] All values are reported in Hz. Spectral data were obtained at 250.13 MHz from a 5 mg/mL solution of **2** in CD_2Cl_2. Chemical shifts are referred to Me_4Si. [b] These coupling constants were assumed to be equal in the calculation. The fit was not significantly improved by removing this assumption. See ref 18.

isomer (ca. 80% of the combined yield of the two products) has been identified as 2-[(bis(ethyloxy)phosphoryl)oxy]-4-chloroacetanilide (**2**) on the basis of its spectral properties[8] and the synthesis of the identical compound from the reaction of 2-hydroxy-4-chloroacetanilide[6] with diethyl chlorophosphite generated in situ from diethyl phosphonate, CCl_4, and triethylamine.[10] Spectal data for the minor product, **3**, definitely indicate that it is an isomer of **2**.[9] Definitive evidence that **3** is 2-chloro-4-[(bis(ethyloxy)-phosphoryl)oxy]acetanilide was provided by the synthesis of a compound identical with **3** from the reaction of 2-chloro-4-hydroxyacetanilide[11] with diethyl chlorophosphite. The combined isolated yield of the two phosphorylated isomers is ca. 3–4%; previously identified products[6] comprise the rest of the product mixture.

The methylene resonance in the ^1H NMR spectrum of **2** in CD_2Cl_2 (Figure 1) is considerably more complicated than that of its isomer, **3**, which shows a simple five-line pattern.[9] In fact, the methylene protons of all structures of the type $R_1R_2X(OCH_2CH_3)_2$ (X = C, P, S) are nonequivalent due to internal asymmetry and would be expected to show a complicated ^1H NMR signal.[12] Several simple compounds of this type, such as diethyl sulfite and acetaldehyde diethyl acetal, have been shown to exhibit methylene proton nonequivalence in their ^1H NMR.[12,13] Most phosphate esters of this type do not exhibit such nonequivalence, and the methylene proton signals of these species can be understood in terms of an A_2C_3X spin system.[14,15] In a few cases, however, it has been necessary to treat the methylene resonance as an ABC_3X case.[14,16] The ^1H NMR spectrum of **2** at 250 MHz was analyzed by the use of the PANIC software[17] on an Aspect 2000 computer as an ABY_3X case.[18] The chemical shifts and coupling constants obtained from the calculation are presented in Table I. The calculated values are consistent with those reported previously for similar compounds,[14b] and Figure 1 shows that the agreement between the observed and calculated methylene resonances is excellent.

Scheme I



Scheme I presents a mechanism for the formation of **2** and **3** which is consistent with the previously observed chemistry of *N*-(sulfonatooxy)acetanilides and related compounds.[6,19,20] Nucleophiles such as Cl^-, Br^-, and H_2O have been shown to attack the solvent separated nitrenium ion–sulfate ion pair derived from **1** at the 2-position,[6] so that attack by the anion of diethyl phosphate on this position is not unexpected. Nucleophilic aromatic substitution of diethyl phosphate on 2-(sulfonatooxy)-4-chloroacetanilide, a known hydrolysis product of **1**,[6] could conceivably lead to **2**.[21] However, control experiments show that this does not occur under the conditions of our study.

Since there is no other source of Cl^- in the system, the minor isomer, **3**, is apparently formed by the attack of the diethyl phosphate anion at the 4-position of the nitrenium ion to generate a hexadienone imine intermediate **4**, which subsequently decomposes into a tight ion pair that col-

(10) Pelletier, S. W.; Locke, D. M. *J. Org. Chem.* **1958**, *23*, 131–133.
(11) Nitration of *m*-chlorophenol yields 3-chloro-4-nitrophenol, which can be separated from its isomer by the procedure of: Hodgson, H. H.; Moore, F. H. *J. Chem. Soc.* **1925**, *127*, 1599–1604. This compound was reduced by the action of $Na_2S_2O_4$ in hot 2 M NaOH according to the procedure of: Hodgson, H. H.; Kershaw, A. *J. Chem. Soc.* **1928**, 2703–2705. The resulting 3-chloro-4-aminophenol was then acetylated with acetyl chloride to yield the necessary acetanilide.
(12) Waugh, J. S.; Cotton, F. A. *J. Phys. Chem.* **1961**, *65*, 562–563.
(13) Finegold, H. *Proc. Chem. Soc.* **1960**, 283–284. Kaplan, F.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 4666–4668. Rattet, L. S.; Mandell, L.; Goldstein; J. H. *Ibid.* **1967**, *89*, 2253–2255.
(14) (a) Siddall, T. H.; Prohaska, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 3467–3473. (b) Williamson, M. P.; Griffin, C. E. *J. Phys. Chem.* **1968**, *72*, 4043–4047.
(15) For example, the methylene resonance of **3** is best treated (at 250 MHz) as an A_2Y_3X case in which $^3J_{HH} = {}^3J_{PH}$.
(16) Finegold, H. *J. Am. Chem. Soc.* **1960**, *82*, 2641–2643.
(17) PANIC is a LAOCOON-type program written for minocomputers by Bruker Instruments, Inc.
(18) An iterative calculation involving seven adjustable parameters was used to fit the calculated methylene and methyl resonances to the experimentally observed frequencies. The adjustable parameters were: ν_{H_a}, ν_{H_b}, ν_{CH_3}, $^3J_{POCH_a} = {}^3J_{POCH_b}$, $^4J_{POCCH_3}$, $^2J_{H_aH_b}$, $^3J_{H_aCCH_3} = {}^3J_{H_bCCH_3}$. No improvement in the fit was found when $^3J_{POCH_a}$ and $^3J_{H_aCCH_3}$ were varied independently of the corresponding coupling constants for H_b. The resulting pairs of coupling constants were equal within ±0.01 Hz under these conditions. The chemical shift of P was held fixed at a value ca. 1500 Hz larger than that of H_a or H_b. Signs of coupling constants cannot be determined since the weak coupling approximation was made. No significant improvement in the fit was observed when this approximation was removed. In the calculation reported here 76 theoretical transitions were assigned to experimental frequencies. The root mean square error was ±0.095 Hz, and the largest error observed was 0.197 Hz.
(19) (a) Novak, M.; Roy, A. K. *J. Org. Chem.* **1985**, *50*, 571–580. (b) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498–1499, 2448–2449.
(20) Pelecanou, M.; Novak, M. *J. Am. Chem. Soc.* **1985**, *107*, 4499–4503.
(21) Manson, D. *Chem.-Biol. Interact.* **1972**, *5*, 47–59.

lapses by internal return. It has been demonstrated in a number of cases that nucleophilic attack at the 4-position of 4-substituted *N*-acyl nitrenium ions by a variety of nucleophiles is a facile process.[19,20] The subsequent rearrangement reaction has not been reported in these systems but would seem to offer a reasonable explanation for the formation of **3**.[22]

The hydrolysis of *N*-(sulfonatooxy)-*p*-acetotoluidide[19a] in the presence of 0.5 M diethyl phosphate also proceeds with the formation of small amounts of previously undetected products. These materials have not yet been isolated in a pure form, but their chromatographic behavior is similar to that of **2** and **3**.

The demonstration that **1** can arylate simple phosphate diesters in aqueous solution may be important to an understanding of the in vivo activity of its polycyclic analogues. We will continue this study with an emphasis on the possible reactions of our model compounds with the phosphate backbone of oligonucleotides in aqueous solution.

Acknowledgment. The high-pressure liquid chromatograph used in this study was purchased with funds obtained from the Cotrell Research Grant Program of the Research Corporation. We are grateful for grant support provided by the American Cancer Society (BC-348). NMR data which were useful in identifying **2** and **3** were obtained at the Worcester Consortium NMR Facility, which is supported by the National Science Foundation (DMR 8108697). High-resolution mass spectra were obtained at the Mass Spectrometry Facility of the Massachusetts Institute of Technology.

(22) A referee has suggested that **3** may be formed from traces of *N*-(sulfonatooxy)-2-chloroacetanilide present in the sample of **1**. We have not been able to detect this material nor have we detected any hydrolysis products which would have arisen from it.

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trans-2-Phenylcyclohexanol. A Powerful and Readily Available Chiral Auxiliary

Summary: The title alcohol has been shown to be a powerful and readily available chiral auxiliary for use in ene reactions of the derived glyoxylate ester.

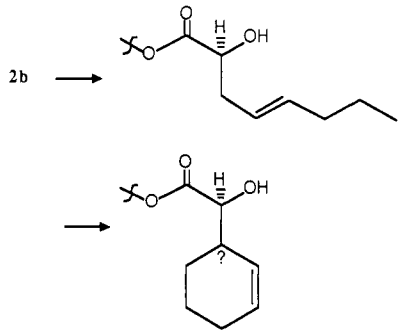
Sir: The control of stereochemistry through the use of asymmetric induction has evolved during the last decade to the point where it is now considered a viable tool within the synthetic arsenal. The chiral auxiliary 8-phenylmenthol (**1a**) has been shown to provide exceptional levels

1 a R = H
b R = OCCHO

2

of induction in a number of reaction processes.[1-3] However, a number of factors[4] combine to seriously limit accessibility to 8-phenylmenthol, and, in addition, access to its enantiomer is even more restricted. We report here that *trans*-2-phenylcyclohexanol (**2a**, PhCy-OH) can be used as a replacement for 8-phenylmenthol and that its preparation in optically active form by enzymatic hydrolysis of its acetate ester provides ready access to both enantiomers.

As part of an extensive investigation of chiral auxiliaries that might mimic the asymmetric induction abilities of 8-phenylmenthol, we investigated the ene reactions of the glyoxylate ester **2b** of *trans*-2-phenylcyclohexanol (PhCyOH, **2a**). Reaction of **2b** with 1-hexene under the



conditions previously found to be optimal for the glyoxylate of 8-phenylmenthol (1 equiv of $SnCl_4$, −78 °C, 1 h) provided a 78% yield of a single diastereomer of the homoallylic alcohol ene adduct by ^{13}C analysis.[5,6] Alternatively, a strictly thermal process (165 °C, 15 h, CH_2Cl_2) provided a 1:1 mixture of the two possible diastereomeric products. The catalyzed reaction of **2b** with cyclohexene also produced a single diastereomer, indicating excellent control of asymmetry at two chiral centers.

While the stereochemical outcomes of the reactions described above are similar to those observed when **1a** was used as chiral auxiliary, such is not the case in the reactions with *cis*- and *trans*-2-butene and with 1-(trimethylsilyl)-*cis*-2-butene where two chiral centers are formed. In these cases the level and direction of stereochemical control at the second center (C-3) differ markedly. Nonetheless, only two of the four possible diastereomers are observed from these reactions,[5] indicating excellent levels of asymmetric induction at C-2.

In addition to the differences noted above in terms of threo to erythro ratios, it was observed that *cis*-butene and *trans*-butene were essentially configurationally stable in the reactions with **2b** (20% isomerization after complete

(1) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(2) Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chim. Acta* **1980**, *63*, 2015. Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Ibid.* **1981**, *64*, 2802. Oppolzer, W.; Loher, H. J. *Ibid.* **1981**, *64*, 2808. Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffatt, F. *Tetrahedron Lett.* **1981**, *22*, 2545.

(3) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 987. Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989. Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.

(4) Whitesell, J. K.; Liu, C.-L.; Buchanan, C. B.; Chen, H. H.; Minton, M. A. *J. Org. Chem.*, submitted for publication.

(5) A nearly equal mixture of diastereomeric ene adducts with this chiral auxiliary were obtained in the absence of the Lewis acid. These isomers are not as well resolved chromatographically as those with 8-phenylmenthol. In all cases, however, the diastereomers show distinct ^{13}C NMR absorptions. Since the minor diastereomers (epimeric at the secondary alcohol carbon) were not observable as products from any of the Lewis acid catalyzed reactions when ^{13}C analysis was carried out with a signal to noise ratio of at least 30:1, we can set a minimum level of induction at 95%.

(6) The structure of all new compounds proposed is based on analysis of ^{13}C and ^{1}H spectral data as well as either elemental analytical or high resolution mass spectral data.

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