Enantiospecific Synthesis of (−)-Tabtoxinine β-Lactam[1]

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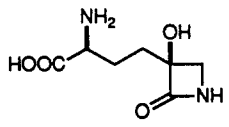
A convergent, 10-step synthesis of optically active tabtoxinine β-lactam [(−)-1] has been described. Key features of the synthetic route include (1) preparation of a new γ-cation amino acid synthon, (−)-4, and its use as an electrophile (3 → 11); (2) the one-pot conversion of methyl sulfide 11 to the Cbz-protected amine 12 via stereoselective sulfilimine rearrangement; and (3) chemoselective lactone ring opening in spiro lactam 15a. Synthons (−)-4 and 3 are available on a semipreparative scale.

Tabtoxinine β-lactam (1) is a potent irreversible inhibitor of glutamine synthetase[2] and has been identified as the causative agent of wildfire disease.[2,3] β-Lactam 1 is unstable in aqueous solution ($t_{1/2}$ = 24 h, pH = 7.0), undergoing intramolecular δ-lactam formation yielding the biologically innocuous isotabtoxinine 2.[3,4] The identification of (L)-glutamic acid as the periodate oxidation product of 1[3] and the total synthesis of (±)-2[5] have permitted the assignment of relative and absolute stereochemistry. In an elegant demonstration of the utility of hetero Diels–Alder chemistry, Baldwin and co-workers have recently described a stereospecific synthesis of (±)-1.[6] Our interest in the design and synthesis of inhibitors of enzymes possessing carboxylate kinase activity[7] prompted disclosure of the preparation and alkylation of azetidine 3, a novel 3-hydroxy β-lactam enolate equivalent i (Scheme I). It was believed that alkylation of 3 with an appropriate γ-cation amino acid equivalent ii would provide access to optically active 1. Herein, we communicate the first total synthesis of (−)-1[8] employing this synthetic strategy.



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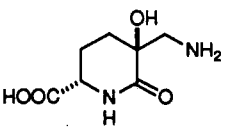

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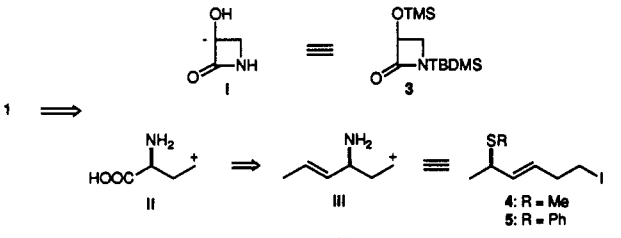
Our first attempt at direct alkylation of 3 with N-protected γ-halo amino acid esters was thwarted by their tendency to undergo racemization and/or intramolecular cyclopropanation as a result of α-deprotonation.[9] This approach was abandoned, and an alternative synthon for the γ-cation amino acid species ii was sought.[10] Retrosynthetic logic led us to consider the electrophilic chiral allylic amine congener iii, where the propenyl group is a latent carboxylate (Scheme I). In devising a suitable synthon, our attention focused upon the report of Tamura[11a] describing the [2,3]-sigmatropic rearrangement of primary allylic *S*-phenylsulfilimines to afford allylic amines. It became apparent from this and related chemistry[11,12] that iii could be represented by a chiral allylic sulfide, 4 or 5, although the stereospecificity of the allylic sulfilimine rearrangement has not been documented.[13]

During the course of this work, we discovered that *a methyl sulfide was essential to the success of the secondary acyclic sulfilimine rearrangement.* We found that allylic phenyl sulfides (e.g., iv) upon reaction with chlor-

Scheme I. Retrosynthetic Analysis for (−)-1



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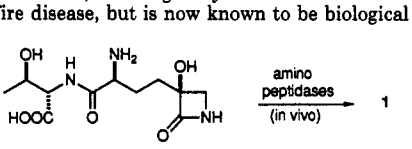
(1) Presented in part at the 201st National Meeting of the American Chemical Society: Li, C.-S.; Dolle, R. E.; Novelli, R.; Kruse, L. I.; Eggleston, D. *Abstracts of Papers*, 201st National Meeting of the American Chemical Society, Atlanta, Georgia; American Chemical Society: Washington, DC, 1991; ORGN 143.

(2) (a) Sinden, S. L.; Durbin, R. D. *Nature* **1968**, *219*, 379. (b) Unkefer, C. J.; London, R. E.; Durbin, R. D.; Uchytil, T. F.; Langston-Unkefer, P. J. *J. Biol. Chem.* **1987**, *262*, 4994. (c) Meek, T. D.; Villafranca, J. J. *Biochemistry* **1980**, *19*, 5513.

(3) (a) Stewart, W. W. *Nature* **1971**, *229*, 174. (b) Tabtoxinine β-lactam (1) is the active component of tabtoxin vi, being derived from vi by the action of peptidases in vivo (Uchytil, T. F.; Durbin, R. D.; *Experientia* **1980**, *36*, 301). Tabtoxin vi, produced by some 40 species of phytopathogenic *Pseudomonas*, was originally believed to be the actual toxic agent of wildfire disease, but is now known to be biological inert.



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(4) Taylor, P. A.; Schnoes, H. K.; Durbin, R. D. *Biochim. Biophys. Acta* **1972**, *286*, 107. Sinden, S. L.; Durbin, R. D. *Phytopathology* **1970**, *60*, 360.

(5) Lee, D. L.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 3491.

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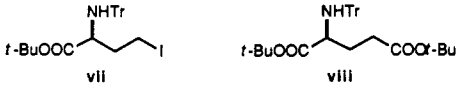
(7) (a) Dolle, R. E; Hughes, M. J.; Li, C.-S.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1989**, 1448. (b) Dolle, R. E.; Hughes, M. J.; Saxty, B.; Wells, T. N. C.; Kruse, L. I.; Eggleston, D. *J. Med. Chem.*, manuscript submitted.

(8) An $[\alpha]_D$ has not been reported for naturally occurring 1. An $[\alpha]^{25}_D$ of −23.7° (*c* 0.22, H_2O) was observed for synthetic 1 (vide infra).

(9) For an example, see: Logusch, E. W. *Tetrahedron Lett.* **1986**, *27*, 5935. Although not attempted, alkylation of 3 with vii may be possible in light of the recent disclosure that the γ-enolate of viii can be formed without loss of optical purity at the α-center: Baldwin, J. E.; North, M.; Flinn, A.; Moloney, M. G. *Tetrahedron* **1989**, *45*, 1453, 1465. Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239.



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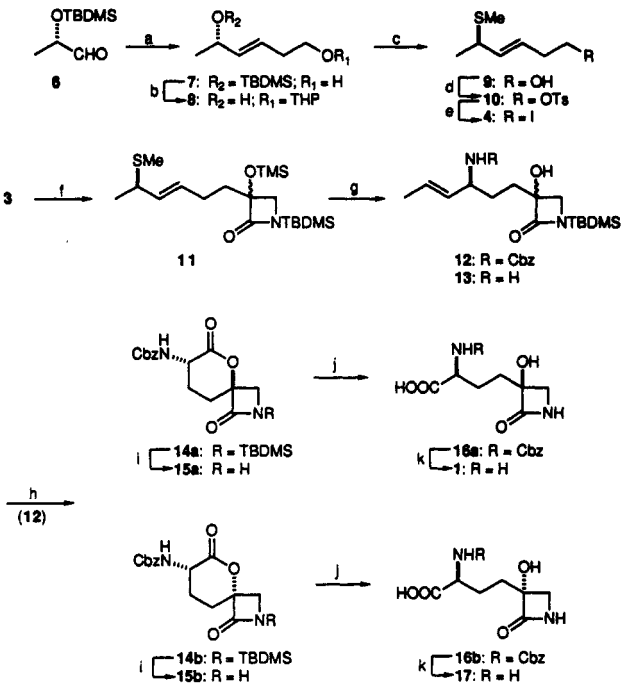
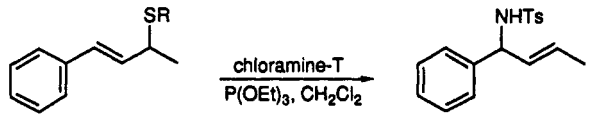
Scheme II. Synthesis of Tabtoxinine β-Lactam [(-)-1][a]



[a] Reagents and conditions: (a) 1.0 equiv of $HO(CH_2)_3PPh_3Cl$, 2.1 equiv of *n*-BuLi, THF, 25 °C, 2 h, 65%; (b) (i) 1.5 equiv of DHP, PPTS (cat.), CH_2Cl_2, 25 °C, 3 h; (ii) 1.5 equiv of *n*-Bu_4NF, THF, 25 °C, 4 h, 92%; (c) (i) 1.2 equiv each of DIAD, TPP, $CH_3C(O)SH$, CH_2Cl_2, 25 °C, 1 h; (ii) 3.0 equiv each of NaOH (5 N aqueous solution), MeI, 0 °C, 30 min; (iii) 0.5% methanolic HCl, 25 °C, 8 h, 54%; (d) 1.5 equiv of TsCl, pyr, 4 °C, 12 h, 64%; (e) 1.5 equiv of NaI, DME, 85 °C, 1 h, 80%; (f) 1.0 equiv of LDA, THF, 1 h, then 1.1 equiv of (-)-4, -78 → 0 °C, 1 h, 88%; (g) 1.1 equiv of *O*-(mesitylenesulfonyl)hydroxylamine, 1.5 equiv of $P(EtO)_3$, CH_2Cl_2, then 4.0 equiv of saturated aqueous $NaHCO_3$ and 1.5 equiv of $PhCH_2OC(O)Cl$, 0 °C, 1 h, 79%; (h) (i) O_3, Sudan III, CH_2Cl_2, -78 °C, then excess Me_2S; (ii) 1.3 equiv of PCC, CH_2Cl_2, 4-Å molecular sieves, 75%; (i) 1.2 equiv of *n*-Bu_4NF, 3.0 equiv of HOAc, THF, 25 °C, 1 h, 84%; (j) 1.1 equiv of NaOH, 3:1 THF-H_2O, 25 °C, 30 min, 75%; (k) 10% Pd/C, 1 atm of H_2, 25 °C, 2 h, 100%.

amine-T[11] undergo amination and rearrangement affording secondary allylic amines to the extent of ca. 10–15%, while the methyl sulfide analogues (e.g., v) yield allylic amines in >90% yield.[14] For this reason, chiral allylic methyl sulfide 4 (not 5) was targeted as our γ-cation amino acid synthon. The requirement of a secondary methyl vs. phenyl sulfide in such systems has not been previously recognized.



Iv: R = Ph — < 15%
v: R = Me — > 90%

Our synthesis of chiral synthon 4 was initiated by the Wittig condensation of (*S*)-(-)-lactaldehyde 6, available in 98% ee on a 100-g scale from (*S*)-(-)-ethyl lactate,[15] with $Ph_3P{=}CHCH_2CH_2OLi$[16] (1.0 equiv, THF, 25 °C, 2 h) to give the *E*-homoallylic alcohol 7 ($[\alpha]^{25}_D$ +0.76° (*c* 1.5, $CHCl_3$)) in 65% yield (20:1 *E*/*Z*, ^1H NMR; Scheme II). Sequential protection of the primary hydroxyl group as its tetrahydropyranyl ether and then desilylation using standard methodology afforded the secondary allylic alcohol 8 (86%). Conversion of 8 to optically active methyl sulfide 9 was accomplished by the following sequence: (1) Mitsunobu inversion using 2 equiv each of diisopropyl azodicarboxylate, triphenylphosphine, and thiolacetic acid[17] (THF, 0 → 25 °C); (2) saponification of the crude thiolacetate in the presence of methyl iodide (MeOH, 3.0 equiv each of NaOH and MeI, 0 °C); (3) acid-catalyzed removal (0.5% methanolic HCl) of the THP protecting group. Sulfide (-)-9, $[\alpha]^{25}_D$ -44.3° (*c* 2.00, $CHCl_3$), was obtained in 54% overall chemical yield from 8 following chromatography. The optical purity of sulfide 9[18] was established to be >95% ee, and the isolated material contained up to 8% of what was believed to be the corresponding S_N2' product (^1H NMR). Iodide 4, $[\alpha]^{25}_D$ -1.8° (*c* 3.4, $CHCl_3$), was readily derived in 60% yield from 9 via the intermediary of *p*-toluenesulfonate 10 (1.2 equiv of *p*-toluenesulfonyl chloride, pyr, 4 °C, 12 h, 64%)[19] and then treatment with NaI (10 → 4; 2.0 equiv of NaI, DME, 85 °C, 1 h, 80%). Synthon (-)-4, a mild lachrymator, was purified by silica gel chromatography (5% Et_2O–petroleum ether) and was stable to storage (neat) for up to 2 weeks at -20 °C. (Sulfide 9 has been stored for >1 year without decomposition.) Multigram quantities (10–15 g) of (-)-4 were routinely prepared using this five-step sequence.[20]

Alkylation of the lithium enolate of 3[7] with iodide (-)-4 (1.2 equiv, -78 → 0 °C, 1 h) occurred smoothly to give 11 in 88% isolated yield as an inseparable 1:1 mixture of C(3) diastereomers (TLC R_f 0.60, silica gel, 10% EtOAc–hex-

(10) α-Cation amino acid synthons: (a) Schollkopf, U.; Neubauer, H. J.; Hauptreif, M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1066. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547 and references therein. (c) Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891. (d) Emert, P.; Meyer, J.; Stucki, C.; Schneebeli, J.; Obrecht, J. P. *Tetrahedron Lett.* **1988**, *29*, 1265. (e) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131. Muster, P.; Steglich, W. *Synthesis* **1987**, 223. A related γ-cation amino acid synthon: Savage, I.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 717.

(11) (a) Tamura, Y.; Sumoto, K.; Minamikawa, J.; Ikeda, M. *Tetrahedron Lett.* **1972**, 4137. Other examples of the allylic sulfilimine rearrangement: (b) Ash, A. S. F.; Challenger, F.; Greenwood, D. *J. Chem. Soc.* **1951**, 1877. (c) Ash, A. S. F.; Challenger, F. *J. Chem. Soc.* **1952**, 2792. (d) Briscoe, P. A.; Challenger, F.; Duckworth, P. S. *J. Chem. Soc.* **1956**, 1755. (e) Tamura, Y.; Matsushima, H.; Minamikawa, J.; Ikeda, M. *Tetrahedron* **1975**, *31*, 3035. (f) Johnson, C. R.; Mori, K.; Nakanishi, A. *J. Org. Chem.* **1979**, *44*, 2065. (g) Tamura, Y.; Ikeda, H.; Chisato, M.; Morita, I.; Ikeda, M. *J. Org. Chem.* **1981**, *46*, 1732.

(12) The [2,3]-sigmatropic rearrangement of allylic selenilimines has been studied by P. B. Hopkins and co-workers: (a) Frankhauser, J. E.; Peevey, R. M.; Hopkins, P. B. *Tetrahedron Lett.* **1984**, *25*, 15. (b) Shea, R. G.; Fitzner, J. N.; Frankhuser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1984**, *49*, 3647. (c) Fitzner, J. N.; Shea, R. G.; Frankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 417. (d) Shea, R. G.; Fitzner, J. N.; Frankhauser, J. E.; Splatenstein, A.; Carpino, P. A.; Peevy, R. M.; Pratt, D. V.; Tenge, B. J.; Hopkins, P. B. *J. Org. Chem.* **1986**, *51*, 5243.* (e) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 3759.

(13) High transfer of stereogenicity was expected to occur on the basis of the precedented stereospecific rearrangement of optically active secondary allylic sulfoxides (see: Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563) and optically active secondary allylic selenilimines (refs 12c,d.)

(14) We had initially considered using the optically active secondary allylic phenyl selenides, but given their difficult construction (see refs 12c,d), these were not pursued.

(15) Masead, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.

(16) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.

(17) Volente, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.

(18) Optical purity was established by conversion of the intermediate thiolacetate to the corresponding Mosher thiolester [(-)-MTPA acid chloride] and 300-MHz ^1H NMR analysis: δ 1.35 [d, 3 H, *J* = 8.0 Hz, (*S*)-C(2)] and δ 1.40 (d, 3 H, *J* = 8.0 Hz, (*R*)-C(2)].

(19) Chromatographic purification of 10 is required to remove all but ca. 3% of the S_N2' material present in iodide (-)-4.

(20) The complementary antipode, (+)-4, was analogously prepared from (*R*)-(+)-6. Access to L- and D-amino acids is therefore possible.

ane). This result was expected on the basis of our earlier work with anion **3**[7] and a model alkylation study of (−)-**4** with other enolate anions.[21] However, our initial attempts to effect the key sulfilimine rearrangement (**11** → **12**) by reaction of **11** with *O*-(mesitylenesulfonyl)hydroxylamine[22] (MSH) and $P(OEt)_3$ were only partly successful.[23] Although the ^1H NMR spectra of crude reaction mixtures clearly demonstrated that the [2,3]-sigmatropic rearrangement had taken place, the intermediate amine **13** was notably unstable, and its attempted isolation, characterization, and protection as the benzyl carbamate (Cbz) derivative failed. After additional experimentation, the critical transformation **11** → **12** was achieved upon exposure of **11** to 1.1 equiv of MSH in CH_2Cl_2 at 0 °C for 1 h, then 1.5 equiv of $P(OEt)_3$ for 15 min followed by the addition of 4.0 equiv of saturated aqueous $NaHCO_3$ and 1.5 equiv of benzyl chloroformate (0 °C, 1 h; in situ carbamoylation). This two-step, one-pot transformation furnished the *N*-Cbz protected amine **12** in 79% isolated yield and occurred with (1) concomitant loss of the *O*-trimethylsilyl protecting group; (2) >85% transfer of stereogenicity during the [2,3]-sigmatropic rearrangement (vide infra);[24] and (3) retention of the β-lactam ring, IR ν_{max} 1740 cm^{-1}.[25] Subsequent ozonolysis of **12** in the presence of Sudan III as an indicator[26] and PCC oxidation of the intermediate lactols provided a 1:1 mixture of diastereomeric spiro lactams (−)-**14a** and (+)-**14b** (70%), TLC R_f 0.35 and 0.40 (silica gel, 30% EtOAc–hexane). Fortuitously, these diastereomers proved readily separable by fractional recrystallization from Et_2O–petroleum ether.[27] X-ray crystallographic analysis of the more polar crystalline (−)-**14a**, mp 138–139 °C, revealed (−)-**14a** to possess the correct (*S*)-C(2′) and (*S*)-C(3) stereochemistry as found in naturally occurring **1** (ORTEP drawing, supplementary material). Fluoride-mediated desilylation of **14a** (**14b**) to **15a** (**15b**) was accomplished in a ca. 85% yield following exposure of **14a** (**14b**) to 1.2 equiv of n-Bu_4NF in THF buffered with 2.5 equiv of glacial acetic acid.

Chemoselective hydrolysis of the δ-lactone ring in spiro lactam **15a** and removal of the Cbz amino-protecting group were the remaining transformations for the synthesis of tabtoxinine β-lactam. Selective hydrolysis was thought possible upon consideration of the X-ray crystal structure of **14a**, where the δ-lactone adopts a twisted boat conformation with atoms C(3), O(3), C(1′), and C(2′) coplanar to within 0.02 Å (see supplementary material). In this conformation the β-lactam carbonyl oxygen points over the top of the lactone ring. This orientation of the β-lactam carbonyl along with the fact that the lactam carbonyl is α,α-disubstituted was thought sufficient to shield the β-lactam carbonyl from attack by hydroxide ion. Selective hydrolysis of the lactone ring in **15a** was observed upon the addition of 1.1 equiv of a 1 N aqueous solution of NaOH in THF–water (3:1; 25 °C, 30 min). Neutralization of the reaction mixture (Dowex 50W×2, H^+ form), filtration, and lyophilization gave **16a** in 75% yield as a single product (^1H NMR).[28] Finally, hydrogenolysis of the Cbz protecting group in water using 10% Pd/C at ambient H_2 pressure followed by removal of the catalyst and lyophilization furnished (−)-**1**, $[\alpha]^{25}_D$ −23.7° (*c* 0.22, H_2O), in quantitative yield.[29] An identical two-step sequence provided (+)-**17**, $[\alpha]^{25}_D$ +35.0° (*c* 0.30, H_2O), from (+)-**15b**.[30]

Although an authentic sample of (−)-**1** was unavailable for direct comparison with our synthetic sample, assignment of the structure of synthetic (−)-**1** as the actual toxin rests with the following: (1) the physical and spectroscopic properties of (−)-**1** are consistent with its formula and are in accord with those reported previously;[3,6,31] (2) the (*S*)-C(2′) and (*S*)-C(3) stereocenters in **14b** [and hence in (−)-**1**] were secured by X-ray crystallographic analysis; and (3) the observed biological activity of synthetic (−)-**1**. Our synthetic material induced chlorosis on tobacco leaves at a minimal concentration of 1 μg/mL and irreversibly inhibited glutamine synthetase, IC_{50} = 3 μg/mL. This activity was identical with that described for naturally occurring **1**.[32] Stereoisomer (+)-**17** was essentially inactive, requiring >1000 μg/mL both to induce chlorosis on tobacco leaves and to inhibit glutamine synthetase.[32]

In summary, a convergent, 10-step synthesis of optically active (−)-tabtoxinine β-lactam has been described. Key features of the synthetic route include (1) preparation of a new γ-cation amino acid synthon, (−)-**4**, and its use as an electrophile (**3** → **11**); (2) the one-pot conversion of methyl sulfide **11** to the Cbz-protected amine **12** via stereoselective sulfilimine rearrangement; and (3) chemoselective lactone ring opening in spiro lactam **15a**. Synthons (−)-**4** and **3** are available on a semipreparative scale, and thus access to gram quantities of (−)-**1** is now possible. Finally, given the demonstrated utility of (−)-**4** as equivalent ii, vis-à-vis iii, other applications of (−)- or (+)-**4** are envisaged.[20,21]

Experimental Section

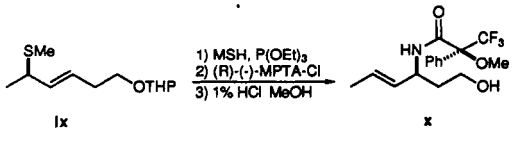
(5*S*,3*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]hex-3-en-1-ol (7). To a suspension of (3-hydroxypropyl)triphenylphosphonium chloride (76.5 g, 0.21 mol; prepared by heating 3-chloropropan-1-ol and triphenylphosphine (1 equiv each) neat at 160 °C for 16 h and recrystallization of the salt from acetonitrile (56% yield)) in THF (500 mL) at 25 °C was added *n*-butyllithium (180 mL

(21) Dolle, R. E.; Osifo, K. I.; Li, C.-S. *Tetrahedron Lett.* **1991**, *32*, 5029.

(22) Tamura, Y.; Minamikawa, J.; Somoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239.

(23) Dolle, R. E.; Li, C.-S.; Shaw, A. N. *Tetrahedron Lett.* **1989**, *30*, 4723.

(24) The stereospecificity of the acyclic [2,3]-sigmatropic rearrangement was investigated in system ix (98% ee). Methyl sulfide ix was transformed to the Mosher amide x [(−)-MPTA acid chloride, pyr; 90% overall yield]. Methoxy resonances were observed at δ 3.39 and 3.42 in a ratio of 8.5:1 (300-MHz ^1H NMR).



ix x

(25) Transacylation of the intermediate allylic amine **13** was not observed under these specific reaction conditions. It is believed that the bulky TBDMS protecting group present on the β-lactam ring and the short reaction time inhibited transacylation.

(26) Veysoglu, T.; Mutscher, L.; Swayze, J. K. *Synthesis* **1980**, 807.

(27) Isomer (−)-**14a** (mp 138–139 °C; $[\alpha]^{25}_D$ −22.8° (*c* 1.15, $CHCl_3$) readily crystallized free from (+)-**14b** (mp 121–122 °C; $[\alpha]^{25}_D$ +52.3° (*c* 0.65, $CHCl_3$). Multiple recrystallizations of (−)-**14a** (ether–petroleum ether) did not change the mp or the magnitude of $[\alpha]_D$. This fact coupled with ^1H NMR data from (−)-**14a** the biological activity of synthetic (−)-**1** (vide infra), and the result recorded in ref 24 argues for the high (>85%) stereoselectivity of the [2,3]-sigmatropic sulfilimine rearrangement. Isomer (+)-**14b** was also isolated in high optical purity.

(28) The remaining 25% of the material was presumably bound to the resin and could not be recovered.

(29) Hydrogenolysis of **15a** (**15b**) in MeOH generated the methyl ester of **1** (**17**) in quantitative yield.

(30) We observed $t_{1/2}$ (**1**) = 5 days and $t_{1/2}$ (**17**) = 21 days at pH 5.5, 25 °C (300-MHz ^1H NMR).

(31) A small sample of (−)-**1** was allowed to rearrange to isotabtoxinine **2** (H_2O, 37 °C, 4 h). The physical and spectroscopic properties of synthetic **2** were in agreement with those reported previously.[7]

(32) We thank Professor J. G. Turner, School of Biological Sciences, University of East Anglia, Norwich, U.K., for conducting the chlorosis-inducing and enzyme assays and for informative discussions.

of a 2.5 M solution in hexanes, 0.45 mol). The mixture was stirred for 1 h, and a homogeneous dark red solution resulted. Aldehyde **6** (40.0 g, 0.21 mol) was added, and the reaction mixture was stirred at 25 °C for 2 h and then quenched with water (50 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (100 mL). The combined organic extracts were evaporated in vacuo. Diethyl ether (200 mL) was added to the residue, and the mixture was stirred at 25 °C for 15 min. The triphenylphosphine oxide which precipitated was removed by filtration. The filtrate was concentrated, and the residue was purified by chromatography (25% Et_2O–petroleum ether) to yield alcohol **7** (32 g, 65%): oil; R_f 0.35 (15% EtOAc–petroleum ether); $[\alpha]^{25}_D$ +0.76° (*c* 1.6, $CHCl_3$); IR (thin film) 3350, 2950, 2920, 2850, 1250, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50 (m, 2 H), 4.24 (m, 1 H), 3.60 (q, 2 H, *J* = 6.5 Hz), 2.25 (q, 2 H, *J* = 6.5 Hz), 1.35 (t, 1 H, *J* = 6.5 Hz), 1.15 (d, 3 H, *J* = 7.0 Hz), 0.85 (s, 9 H), 0.05 (s, 6 H); mass spectrum, *m/e* 173 ($M^+ - Me_3C$) 146, 131, 75. Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.50; H, 11.33.

(5*S*,3*E*)-1-[(Tetrahydro-2*H*-pyran-2-yl)oxy]hex-3-en-5-ol (8). To a solution of alcohol **7** (21.0 g, 91.0 mmol) and dihydropyran (14.0 mL, 0.15 mol) in CH_2Cl_2 (100 mL) were added successively pyridinium *p*-toluenesulfonate (500 mg) and *p*-toluenesulfonic acid (100 mg). The mixture was stirred at 25 °C for 3 h, washed with saturated $NaHCO_3$ (100 mL), and dried ($MgSO_4$), and the solvents were removed in vacuo.

The residue obtained above was dissolved in THF (120 mL), and *n*-Bu_4NF (120 mL of a 1 M solution in THF) was added. The reaction mixture was stirred at 25 °C for 4 h, and the solvent was removed in vacuo. The residue was diluted with water (200 mL) and extracted with Et_2O (3 × 150 mL). The combined ethereal extracts were washed with water (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (50% Et_2O–petroleum ether) to furnish alcohol **8** (16.8 g, 92% from **7**): oil; R_f 0.35 (30% EtOAc–petroleum ether); IR (thin film) 3420, 2940, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.60 (m, 2 H), 4.60 (m, 1 H), 4.25 (m, 1 H), 3.90–3.30 (m, 4 H), 2.35 (q, 2 H, *J* = 6.5 Hz), 1.90–1.40 (m, 6 H), 1.25 (d, 3 H, *J* = 7.0 Hz); mass spectrum, *m/e* 115 ($M^+ - C_5H_9O$), 101, 85. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.89; H, 10.05.

(5*R*,3*E*)-5-(Methylthio)hex-3-en-1-ol (9). To a solution of triphenylphosphine (40.6 g, 0.15 mol) in THF (420 mL) at 0 °C was added dropwise diisopropyl azodicarboxylate (31.3 g, 0.15 mol) over a period of 15 min. The mixture was stirred at 0 °C for 1 h, and a white precipitate was observed. A solution of allylic alcohol **8** (15.5 g, 78.0 mmol) and thiolacetic acid (11.5 mL, 78.0 mmol) in THF (200 mL) was then added over a 15-min period. The mixture was stirred at 0 °C for 1 h and then at 25 °C for 1 h, and the solvent was removed in vacuo. The residue was triturated with Et_2O–petroleum ether (1:1, 400 mL), and the resulting suspension was stirred at 25 °C for 15 min. The solution was filtered and the filtrate concentrated in vacuo. This trituration/filtration/concentration process was repeated a second time. The residue so obtained was passed through a plug of silica gel (10% Et_2O–petroleum ether) to yield the intermediate thiolacetate (18 g).

The crude thiolacetate (18 g) was dissolved in MeOH (300 mL) containing CH_3I (15.0 mL, 0.24 mol). A 5 N aqueous solution of NaOH (50 mL, 0.25 mol) was added at 0 °C, and the mixture was stirred for 30 min. The solvent was evaporated in vacuo, and the residue was diluted with water (200 mL) and extracted with Et_2O (2 × 150 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was filtered through a plug of silica gel (15% Et_2O–petroleum ether) to yield the corresponding intermediate methyl sulfide (10.2 g).

The mehyl sulfide obtained above was dissolved in MeOH (200 mL), and 12 N HCl (1 mL) was added. The reaction mixture was stirred at 25 °C for 8 h, and the solvent was removed in vacuo. The residue was purified by chromatography (30% Et_2O–petroleum ether, then 50% Et_2O–petroleum ether) to yield sulfide **9** (6.0 g, 54% from **8**): oil; R_f 0.40 (silica gel, 30% EtOAc–petroleum ether); $[\alpha]^{25}_D$ −44.3° (*c* 2.0, $CHCl_3$); IR (thin film) 3360, 2980, 2920, 1440, 1100, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (m, 2 H), 3.65 (t, 2 H, *J* = 7.0 Hz), 3.20 (m, 1 H), 2.35 (q, 2 H, *J* = 7.0 Hz), 2.00 (s, 3 H), 1.30 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 134.9 (s), 126.4 (s), 62.0 (d), 43.4 (s), 35.5 (d), 20.7 (t), 13.8 (t); mass spectrum, *m/e* 146 (M^+), 98, 81, 69, 67, 55, 53, 41, 39. Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.64. Found: C, 57.52; H, 9.63.

(5*R*,3*E*)-1-Iodo-5-(methylthio)hex-3-ene (4). A solution of sulfide **9** (12.1 g, 83 mmol) and *p*-toluenesulfonyl chloride (24.0 g 0.25 mmol) in pyridine (50 mL) was stored at 4 °C for 12 h. Water (150 mL) was added, and the mixture was extracted with Et_2O (2 × 150 mL). The combined ethereal extracts were washed with cold 1 N aqueous HCl (2 × 250 mL) and brine (150 mL) and dried (Na_2SO_4), and the Et_2O was evaporated. The residue was purified by chromatography (20% Et_2O–petroleum ether, then 75% Et_2O–petroleum ether) to afford tosylate **10** (16 g, 64%).

Tosylate **10** was dissolved in a 1 M solution of NaI in DME (140 mL, 140 mmol of NaI), and the solution was heated at reflux for 1 h. After cooling, water (200 mL) was added, and the mixture was extracted with Et_2O (400 mL). The ethereal extract was washed with 1 M aqueous sodium thiosulfate (100 mL) and water (100 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (5% Et_2O–petroleum ether) afforded optically active iodide (−)-**4** (10.7, 50% from **9**): pale yellow oil (lachrymator, odor of burning rubber); R_f 0.70 (5% EtOAc–petroleum ether); $[\alpha]^{25}_D$ −1.8° (*c* 3.40, $CHCl_3$); IR (thin film) 2980, 2910, 1420, 1330, 1300, 1260, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.40 (m, 2 H), 3.20 (m, 3 H), 2.60 (m, 2 H), 2.00 (s, 3 H), 1.35 (d, 3 H, *J* = 7.0 Hz); mass spectrum, *m/e* 256 (M^+), 209, 129. Anal. Calcd for $C_7H_{13}IS$: C, 32.82; H, 5.11. Found: C, 32.79; H, 5.10.

(3*RS*,3′*E*,5′*R*)-1-(*tert*-Butyldimethylsilyl)-3-[5′-(methylthio)hex-3′-enyl]-3-[(trimethylsilyl)oxy]-2-oxoazetidine (11). A solution of azetidinone **3**[7b] (10.2 g, 37.3 mmol) in THF (10 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (15.0 mL, 2.5 M in hexanes, 37.5 mmol) to a solution of diisopropylamine (6.0 mL, 42.9 mmol) in THF (150 mL)) at −78 °C over a period of 10 min. The reaction mixture was stirred at −78 °C for 1 h to ensure complete anion formation. Iodide **4** (10.2 g, 39.8 mmol) was added in one portion, and the mixture was slowly warmed to 0 °C over a period of 2 h and then quenched with water (10 mL). Following further dilution with water (250 mL), the mixture was extracted with Et_2O (2 × 200 mL). The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue so obtained was purified by chromatography (6% Et_2O–petroleum ether) to give azetidinone **11** (13.2 g, 88%): oil; R_f 0.60 (silica gel, 10% EtOAc–petroleum ether); IR (thin film) 2940, 2840, 1745, 1465, 1250, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.40 (m, 2 H), 3.20 (m, 3 H), 2.20 (m, 2 H), 2.00 (s, 3 H), 1.90 (m, 2 H), 1.30 (d, 3 H, *J* = 7.0 Hz), 0.95 (s, 9 H), 0.26 (s, 3 H), 0.25 (s, 3 H), 0.20 (s, 6 H); mass spectrum, *m/e* 406 (M^+ + H), 354. Anal. Calcd for $C_{19}H_{39}NO_2SSi_2$: C, 56.80; H, 9.78; N, 3.49. Found: C, 57.05; H, 9.92; N, 3.39.

(3*RS*,3′*S*,4′*E*)-1-(*tert*-Butyldimethylsilyl)-3-[3′-(benzyloxycarbonyl)amino]hex-4′-enyl]-3-hydroxy-2-oxoazetidine (12). A solution of sulfide **11** (13.2 g, 32.9 mmol) in CH_2Cl_2 (66 mL) was treated with *O*-(mesitylenesulfonyl)hydroxylamine[22] (7.8 g, 36.2 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 1 h. Triethylphosphite (8.0 mL, 48.0 mmol) was added, and the mixture was stirred at 25 °C for 15 min. After cooling to 0 °C, saturated aqueous $NaHCO_3$ (132 mL) was added followed by the addition of benzyl chloroformate (7.5 mL, 50.0 mmol). The reaction mixture was vigorously stirred at 0 °C for 1 h. The organic layer was separated and dried (Na_2SO_4), and following the addition of triethylamine (7.0 mL, 50 mmol), the solvents were removed in vacuo. The residue was purified by chromatography (30% EtOAc–petroleum ether and then 50% EtOAc–petroleum ether) to afford benzyl carbamate **12** (11.2 g, 79%): oil; R_f 0.30 (30% EtOAc–petroleum ether); IR (thin film) 3320, 1740, 1720, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 5.70–5.25 (m, 2 H), 5.10 (s, 2 H), 4.90 (2 d, NH of two diastereomers, 1 H), 4.20 (br s, 1 H), 3.90 (br s, 1 H), 3.22 (m, 2 H), 2.0–1.60 (m, 4 H), 1.65 (d, 3 H, *J* = 7.0 Hz), 0.95 (s, 9 H), 0.21 (s, 3 H), 0.20 (s, 3 H); mass spectrum, *m/e* 433 (M + H), 372, 282, 184, 160, 140, 124. Anal. Calcd for $C_{23}H_{36}N_2O_4Si$: C, 63.85; H, 8.39; N, 6.48. Found: C, 63.38; H, 8.37; N, 6.09.

(3*S*,3′*S*)-1-(*tert*-Butyldimethylsilyl)-3-[3′-[(benzyloxycarbonyl)amino]-3′-carboxypropyl]-3-hydroxy-2-oxoazetidine δ-Lactone (14a) and the 3*R*,3′*S* Diastereomer (14b). A solution of benzyl carbamate **12** (4.4 g, 10.2 mmol) in MeOH (120 mL) containing Sudan III (0.1 mg as an indicator) was cooled to −78 °C. Ozone was passed into the orange-red colored solution

until the solution became colorless. Methyl sulfide (3.0 mL) was added, and the mixture was warmed to 25 °C. The mixture was stirred for 2 h (orange-red color reappeared), and the solvent was evaporated to furnish the crude diastereomeric lactols, which were oxidized directly.

To a suspension of pyridinium chlorochromate (4.4 g, 20.4 mmol), powdered 4-Å molecular sieves (10 g), and anhydrous NaOAc (300 mg) in CH_2Cl_2 (50 mL) was added a solution of the crude lactols in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 25 °C for 3 h, and then the mixture was poured onto a column of silica gel (150 g). The column was eluted with 50% EtOAc–petroleum ether to give a 1:1 mixture of spiro lactams **14a** and **14b** (3.11 g). The spiro lactams were dissolved in 5% Et_2O–petroleum ether (10–15 mL) and stored at 4 °C overnight. A white solid (R_f 0.35, 30% EtOAc–petroleum ether) was obtained and collected by filtration. Recrystallization (Et_2O–petroleum ether) of the material gave lactone **14a** (880 mg, 21%) as white needles. For **14a**: mp 138–139 °C; R_f 0.35 (silica gel, 30% EtOAc–petroleum ether); $[\alpha]^{25}_D$ −22.8° (*c* 1.15, $CHCl_3$); IR (Nujol) 2920, 1750, 1730, 1710, 1460, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (br s, 5 H, Ar), 5.50 (br d, 1 H), 5.10 (s, 2 H), 5.05 (m, 1 H), 3.55 (d, 1 H, *J* = 7.0 Hz), 3.35 (d, 1 H, *J* = 7.0 Hz), 2.70 (m, 1 H), 2.30 (m, 2 H), 1.75 (m, 1 H), 0.95 (s, 9 H), 0.25 (s, 6 H); ^{13}C NMR (CD_3OD) δ 179.2 (q), 174.3 (q), 158.6 (q), 138.2 (q), 129.5 (s), 129.2 (s), 128.8 (s), 86.0 (q), 67.7 (d), 55.5 (s), 54.3 (d), 32.5 (d), 27.1 (d), 26.4 (t), 19.4 (q), −6.1 (t); mass spectrum, *m/e* 419 (M + H). Anal. Calcd for $C_{21}H_{30}N_2O_5Si$: C, 60.26; H, 7.22; N, 6.69. Found: C, 60.34; H, 7.20; N, 6.58.

The filtrate was concentrated and repeatedly purified by chromatography (50% EtOAc–petroleum ether) to provide diastereomer **14b** (1.0 g, 23%). An analytical sample of **14b** was obtained upon recrystallization from Et_2O–petroleum ether. For **14b**: mp 121–122 °C; R_f 0.40 (silica gel, 30% EtOAc–petroleum ether); $[\alpha]^{25}_D$ +52.3° (*c* 0.65, $CHCl_3$); IR (Nujol) 2920, 1745, 1710, 1460, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H, Ar), 5.70 (d, 1 H, *J* = 8.5 Hz), 5.10 (s, 2 H), 4.35 (m, 1 H), 3.45 (dd, 2 H, *J* = 16.5, 7.0 Hz), 2.50–2.00 (m, 4 H), 0.95 (s, 9 H), 0.25 (s, 3 H), 0.22 (s, 3 H); ^{13}C NMR (CD_3OD) δ 179.8 (q), 175.3 (q), 158.6 (q), 138.1 (q), 129.5 (s), 129.0 (s), 128.8 (s), 85.7 (q), 68.1 (d), 55.4 (s), 54.4 (d), 32.3 (d), 27.2 (d), 26.3 (t), 19.4 (q), −6.1 (t); mass spectrum, *m/e* 418 (M^+), 261, 233, 91. Anal. Calcd for $C_{21}H_{30}N_2O_5Si$: C, 60.26; H, 7.22; N, 6.69. Found: C, 60.30; H, 7.07; N, 6.55.

(3*S*,3′*S*)-3-[3′-[(Benzyloxycarbonyl)amino]-3′-carboxypropyl]-3-hydroxy-2-oxoazetidine δ-Lactone (15a) and the 3*R*,3′*S* Diastereomer (15b). A solution of lactone **14a** (660 mg, 1.60 mmol) in THF (3 mL) containing glacial acetic acid (0.3 mL, 5.0 mmol) was treated with *n*-Bu_4NF (1.9 mL of a 1 M THF solution, 1.9 mmol). The mixture was stirred for 1 h, and then solvents were removed in vacuo. Purification of the residue by chromatography (1% MeOH–EtOAc) gave lactone **15a** (405 mg, 84%): foam; R_f 0.50 (EtOAc); IR (Nujol) 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5.90 (br s, 1 H), 5.55 (br s, 1 H), 5.10 (s, 2 H), 5.00 (m, 1 H), 3.70 (d, 1 H, *J* = 7.0 Hz), 3.45 (d, 1 H, *J* = 7.0 Hz), 2.70 (m, 1 H), 2.35 (m, 2 H), 1.80 (m, 1 H); mass spectrum, *m/e* 305 (M + H), 261, 91; high-resolution FAB mass spectrum calcd for $C_{15}H_{16}N_2O_5$ 304.2790, found 304.2780.

Lactone **15b** was prepared by analogous desilylation of intermediate lactone **14b**. For **15b**: foam; R_f 0.5 (EtOAc); IR (Nujol) 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 6.10 (br s, 1 H), 5.62 (d, 1 H, *J* = 8.5 Hz), 5.10 (s, 2 H), 4.35 (m, 1 H), 3.55 (m, 2 H), 2.60–2.05 (m, 4 H); mass spectrum, *m/e* 305 (M + H); high-resolution FAB mass spectrum calcd for $C_{15}H_{16}N_2O_5$ 304.2790, found 304.2775.

(3*S*,3′*S*)-3-(3′-Amino-3′-carboxypropyl)-3-hydroxy-2-oxoazetidine (Tabtoxinine β-Lactam) (1) and the 3*R*,3′*S* Diastereomer (17). To a solution of spiro lactam **15a** (760 mg, 2.5 mmol) in THF–H_2O (3:1, 20 mL) was added 1 N aqueous NaOH (3 mL, 3.0 mmol). The solution was stirred at 25 °C for 30 min and then neutralized with an acidic ion-exchange resin (Dowex 50W×2, 100–200 mesh, Biorad). The suspension was filtered, and the solvents were evaporated in vacuo. The residue was dissolved in a small portion of water and lyophilized to yield *N*-Cbz protected tabtoxinine β-lactam **16a** (590 mg, 75%) as a white powder. The remaining material (25%) was not recovered from the resin.

Acid **16a** so obtained was dissolved in water (40 mL) to which 10% Pd/C (40 mg) was added. The suspension was stirred under ambient H_2 pressure for 2 h. The reaction mixture was filtered and the filtrate lyophilized to afford analytically pure tabtoxinine β-lactam **1** (38 mg, 100% foam **16a**): amorphous white solid; R_f 0.35 (silica gel, 2:1:1 *n*-BuOH–HOAc–H_2O); $[\alpha]^{25}_D$ −23.7° (*c* 0.30, H_2O); IR (KBr) 3420, 3250, 1745, 1630 cm^{-1}; ^1H NMR (D_2O) δ 3.75 (m, 1 H), 3.50 (d, 1 H, *J* = 7.0 Hz), 3.35 (d, 1 H, *J* = 7.0 Hz), 2.20–1.70 (m, 4 H); ^{13}C NMR (D_2O) δ 181.8 (q), 176.5 (q), 72.7 (q), 59.8 (s), 49.5 (d), 33.2 (d), 25.5 (d); mass spectrum, *m/e* 189 (M + H). Anal. Calcd for $C_7H_{12}N_2O_4$: C, 76.58; H, 6.42; N, 14.88. Found: C, 76.50; H, 6.40; N, 14.52.

The corresponding 3*R*,3′*S* diastereomer **17** was obtained in analogous fashion from **15b** via intermediate **16b**. For **17**: amorphous white solid; R_f 0.35 (silica gel, 2:1:1 *n*-BuOH–HOAc–H_2O); $[\alpha]^{25}_D$ +35.0° (*c* 0.22, H_2O); IR (Nujol) 3340, 1720, 1620 cm^{-1}; ^1H NMR (D_2O) δ 3.80 (m, 1 H), 3.50 (d, 1 H, *J* = 7.0 Hz), 3.35 (d, 1 H, *J* = 7.0 Hz), 2.20–1.80 (m, 4 H); ^{13}C NMR (D_2O) δ 181.8 (q), 176.3 (q), 72.1 (q), 60.1 (s), 49.6 (d), 34.4 (d), 25.6 (d); mass spectrum, *m/e* 189 (M + H). Anal. Calcd for $C_7H_{12}N_2O_4$: C, 76.58; H, 6.42; N, 14.88. Found: C, 76.48; H, 6.37; N, 14.89.

Supplementary Material Available: Experimental details of the X-ray structure determination of (−)-**14a**, ORTEP representation of (−)-**14a**, and tables of fractional atomic coordinates, thermal parameters, and interatomic distances and angles for (−)-**14a** (12 pages). Ordering information is given on any current masthead page.

Synthesis of Partially Fluorinated Analogues of (*Z*)-5-Decenyl Acetate: Probes for Hydrophobic Interaction in Pheromone Reception

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Selective regiochemical introduction of fluorines into methyl and methylene positions of (*Z*)-5-decenyl acetate provides analogues to probe the hydrophobicity requirements of the pheromone receptor site in the turnip moth, *Agrotis segetum*. Perfluorobutyl-, difluoromethylene-, trifluoromethyl-, and tetrafluoroethylene-containing analogues have been synthesized and chemically characterized.

Straight-chain monofunctionalized alkenes with a *Z* double bond constitute by far the largest class of known pheromone components produced by female moths (Insecta, Lepidoptera).[1] Each pheromone component is

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