Preparation of 15-iso-10. To a solution of 0.0097 g (0.018 mmol) of crystalline **26** in 2 mL of THF at 0 °C was added 0.05 mL (0.05 mmol, 2.5 molar equiv) of a 1.0 M solution of tetrabutylammonium chloride in THF. The mixture was stirred at 0 °C for 30 min, 10 mL of water was added, and the mixture was extracted with ethyl acetate (1 × 10 mL, 2 × 5 mL). The combined organic layers were washed with water (2 × 15 mL), followed by saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 0.0065 g (94%) of a colorless oil. TLC and ^1H NMR analysis indicated the succinylated α-hydroxy enedione, with the same TLC mobility as authentic A26771B (10% MeOH/$CHCl_3$, R_f 0.385); however, the vinyl proton chemical shift was slightly shifted. An analytical sample was prepared by taking up the oil in a minimum of acetone and triturating with a large amount of water to give a white amorphous solid: ^1H NMR (270 MHz, $CDCl_3$) (all signals identical with A26771B except for vinyl resonances) δ 1.30 (d, J = 6.3 Hz, ca. 3 H), 1.2-1.4 (br m, ca 14 H), 1.61 (m, 2 H), 1.87 (m, 2 H), 2.75 and 2.77 (m, with 2 s, 4 H), 5.09 (m, with 4 sharp lines, 1 H), 5.36 (t, J = 5.5 Hz, 1 H), 6.76 (d, J = 15.8 Hz, 1 H), 7.16 (d, J = 15.8 Hz, 1 H), 10-11 (br s, 1 H, CO_2H); IR ($CHCl_3$) 3600-3000, 1744, 1736, 1722, 1713 cm^{-1}; mass spectrum of **10**, 15-iso-**10** mixture m/e (rel intensity) (no molecular ion observed) 293 (0.2), 281 (0.2), 231 (0.9), 181 (3.9) 119 (8), 69 (44), 44 (100).

Preparation of 10. According to the procedure given above, 0.0415 g (0.08 mmol) of a 3:1 **25**:**26** mixture was treated with 0.3 mmol of tetrabutylammonium fluoride in THF, at room temperature for 3 h, to give, after aqueous workup, 0.0295 g (95%) of a colorless oil, which solidified on standing. Addition to acetone (1 mL) and 25 mL of water produced the precipitation of a 3:1 mixture of pure **10**:15-iso-**10** as a white solid, mp 112-116 °C. The ^1H NMR signals for **10** were superimposable on the 270-MHz ^1H NMR spectrum of authentic A26771B. TLC analysis in 5% methanol/chloroform, 10% methanol/chloroform, and 100% ethyl acetate had identical mobilities with the natural product. Attempted recrystallization from ethyl acetate/hexane was unsuccessful.

Acknowledgment. We are grateful for the continuing support of our programs by the General Medical Sciences Institute of the National Institutes of Health. S.J.B. thanks NIH for the award of a postdoctoral fellowship. Our appreciation and thanks are extended to Dr. Paul De Marco of Eli Lilly Laboratories for a generous authentic sample of antibiotic A26771B and Dr. David Pensak for collaborating in the molecular mechanics calculations.

Registry No. (±)-**10**, 77449-88-8; (±)-15-iso-**10**, 84026-48-2; **11**, 83999-33-1; **12**, 112-45-8; (±)-**13**, 83999-34-2; (±)-**14**, 83999-35-3; (±)-**15**, 83999-36-4; (±)-**16**, 84009-44-9; **17**, 83999-37-5; **18**, 83999-38-6; **19**, 83999-39-7; (±)-**21** (isomer 1), 83999-40-0; (±)-**21** (isomer 2), 84026-49-3; (±)-**24** (isomer 1), 84009-45-0; (±)-**24** (isomer 2), 84048-16-8; (±)-**25**, 83999-41-1; (±)-**26**, 84026-50-6; ethyl vinyl ether, 109-92-2; benzenesulfonylacetic acid, 3959-23-7; succinic anhydride, 108-30-5.

Total Synthesis of the Paniculides

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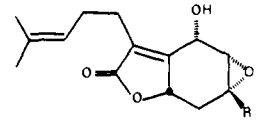
Contribution from the Department of Chemistry, the Laboratory for Research on the Structure of Matter, and the Monell Chemical Senses Center, The University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received May 27, 1982*

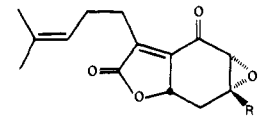
Abstract: In this, a full account, we disclose the first total synthesis of paniculides A-C (**1-3**), three highly oxygenated sesquiterpenes isolated in 1968 by Overton et al. from hypocotyl and stem tissue cultures of *Andrographis paniculata*. Our approach, which is both highly efficient and stereocontrolled and furthermore serves to confirm for the *first time* the structural assignments of the paniculides, begins with the facile photochemical [2 + 2] cycloaddition of enones **12** and **13** to 1,1-diethoxyethylene. Application of the Kochi-McMurry $Pb(OAc)_4$-induced oxidative decarboxylation on the derived carboxylic acid **9a** and the Saegusa protocol on **9b** afforded bicyclic ketones **8a** and **8b**, respectively, the concave-convex nature of which provides the needed stereochemical bias required to introduce the epoxide oxygen. Toward the latter end, reduction ($NaBH_4/CeCl_3$) of each followed by *m*-CPBA oxidation led to a 3:1 mixture of epoxy lactones. Protection of the C(15)-hydroxyl of the major lactone in each case (i.e., **6a** and **6b**) as the triethylsilyl (TES) ether and alkylation with 2-methyl-5-iodo-2-pentene gave **22a** and **22b**, respectively. Final introduction of the C(6,7) unsaturation via the Reich-Sharpless oxidative elimination protocol and removal of the TES protecting group afforded racemic paniculide A and B, respectively. Oxidation of the C(8)-hydroxyl in both cases then afforded paniculides C (**3**) and D (**4**), the latter a likely, albeit as yet unknown, natural product. The overall efficiency to paniculides A and B from enones **12** and **13**, respectively, was 5.5 and 3.6%. Finally, two significant observations emanated from this venture. First, potassium amide bases [i.e., $KN(SiMe_3)$] are more effective in the deprotonation of highly oxygenated systems than the corresponding lithium amide bases. Second, the utility of diphenyl diselenide as an electrophile can be greatly improved simply by oxidation of the selenenylation reaction mixture prior to workup.

Introduction and Background

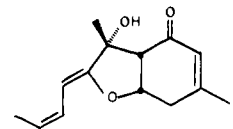
In 1968, during the course of phytochemical studies of callus cultures derived from *Andrographis paniculata* Nees,[1,2] Overton et al. at the University of Glascow disclosed the isolation of three highly oxygenated sesquiterpenoids termed paniculides A, B, and C (**1-3**, respectively) that were related to bisabolangelone (**5**).[3] Structural assignments were based on elemental composition data, in conjunction with spectroscopic properties including ^1H and ^{13}C NMR as well as mass spectrometric fragmentation patterns. Interestingly, while these novel sesquiterpenoids have been known for well over a decade, their structures at the outset of our work had yet to be confirmed either by X-ray analysis or by total synthesis. Indeed, to the best of our knowledge, there has been only one report concerning construction of the basic carbocyclic skeleton; this is the work of Jacobi at Wesleyan.[4]



1: Paniculide A, R = Me
2: Paniculide B, R = CH_2OH



3: Paniculide C, R = CH_2OH
4: Paniculide D, R = Me



5: Bisabolangelone

(1) Allison, A. J.; Butcher, D. N.; Connolly, J. D.; Overton, K. H. *J. Chem. Soc., Chem. Commun.* **1968**, 1493.
(2) Butcher, D. N.; Connolly, J. D. *J. Exp. Bot.* **1971**, *22*, 314.
(3) Novotny, L.; Samek, Z.; Sorm, F. *Tetrahedron Lett.* **1966**, 3541.

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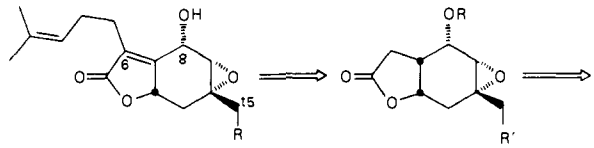
Our interest in the paniculides stemmed from their close structural similarity to a number of pharmacologically important sesquiterpenes including vernolepin[5] and eriolanin.[6] In particular, each system is highly oxygenated, possesses a lactone ring with adjacent oxygen functionality, and is endowed with stereochemical centers that punctuate the periphery of a six-membered ring.

In this, a full account, we record the first total synthesis of paniculides A–C[7,8] as well as paniculide D, a likely albeit as yet unknown natural product. We note in advance that our initial goal of developing a common synthetic strategy that would in turn lead to each of the paniculides has been achieved. Significantly, each synthesis is short, highly efficient, and stereocontrolled. Furthermore, it serves for the *first time* to confirm the structural assignments of the paniculides.[9] Finally, two potentially significant observations concerning the deprotonation and selenenylation of highly oxygenated systems emanated from this venture (vide infra).

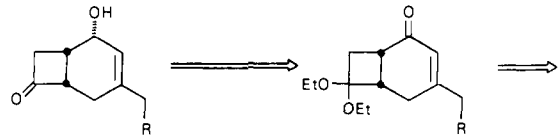
Results and Discussion

(i) A Common Strategy for Construction of the Paniculides. From the retrosynthetic perspective, intermediates **8a** and **8b**, both presumably available after modest functional-group manipulation of initially generated [2 + 2] photochemical cycloadducts **9a** and **9b**, respectively, appeared ideal as precursors for the paniculide nuclei **6a** and **6b**. Central to this scenario is the concave–convex nature of the bicyclooctenone intermediate **8**, the latter providing the needed stereochemical bias required to introduce the epoxide oxygen relative to the protected cyclobutanone ring.[10] The cyclobutanone unit in turn was anticipated to serve as a latent γ-lactone (Baeyer–Villiger oxidation)[11] and eventually as the butenolide ring system. Final introduction of both side chain and unsaturation then appeared straightforward, assuming, of course, that the regiochemical problem associated with unsaturation introduction could be solved. Our plan here called for utilization of the Reich–[12a]Sharpless[12b] phenylselenenylation oxidative-elimination protocol. For success, two prerequisites were mandatory. First the hydrogen at C(7) and the phenyl selenoxide group in **10** must have a cis disposition. To set this stereochemistry, we



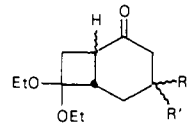
1: Paniculide A, R = H
2: Paniculide B, R = OH

6a: R = H, R' = H
b: R = H, R' = $OSiMe_2{}^tBu$
c: R = TES, R' = H
d: R = TES, R' = $OSiMe_2{}^tBu$

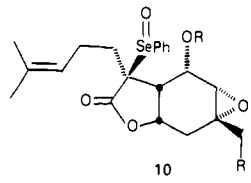


7a: R = H
b: R = $OSiMe_2{}^tBu$

8a: R = H
b: R = $OSiMe_2{}^tBu$



9a: R = Me, R' = COOMe
b: R = H, R' = $CH_2OSiMe_2{}^tBu$



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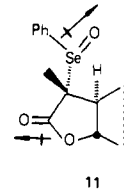
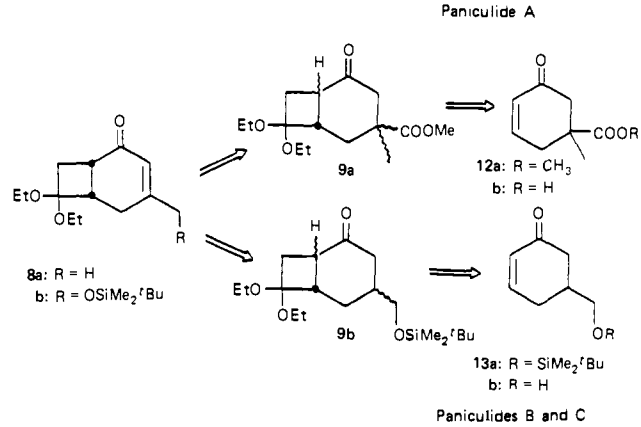


11

again anticipated taking advantage of the concave–convex nature of the paniculide nuclei (i.e., **6**). Second, thermal elimination of PhSeOH must proceed to afford the endo and not the exo olefin. Here, as first pointed out by Trost,[13] the dipole moment of the lactone carbonyl and that of the selenoxide (in his case sulfoxide) will align in such a fashion as to direct the oxygen of the selenoxide toward the endo hydrogen (cf. **11**).

Continuing with the retrosynthetic analysis, we envisioned construction of the requisite bicyclo[4.2.0]octanone system (**9a** and **9b**) via a [2 + 2] photocycloaddition reaction between an



appropriate enone (cf. **12a** and **13a**) and 1,1-diethoxyethylene.[14]

(4) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. See also: Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611.

Note Added in Proof: Recently Yoshikoshi et al. of Tokoku University (Sendi) completed an alternate synthesis of paniculide A; see: Kido, F.; Noda, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1209.

(5) Kupchan, S. M.; Baxter, R. L.; Chiang, C. K.; Gilmore, C. J.; Bryan, R. F. *J. Chem. Soc., Chem. Commun.* **1973**, 842. For synthesis of vernolepin, see: (a) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773. (b) Danishefsky, S.; Kitchara, T.; Schuda, P. F.; Etheredge, S. J. *Ibid.* **1976**, *98*, 3028. (c) Kieczykowski, G. R.; Schlessinger, R. H. *Ibid.* **1978**, *100*, 1938. (d) Isobe, M.; Iio, H.; Kawai, T.; Goto, T. *Ibid.* **1978**, *100*, 1940.

(6) Kupchan, S. M.; Hemingway, R.; Werner, D.; Karim, A.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 3596. For synthesis of eriolanin, see: Grieco, P. A.; Oguri, T.; Gilman, S.; DeTitta, G. T. *Ibid.* **1978**, *100*, 1616.

(7) A preliminary account of the paniculide A synthesis was presented at the National meeting of the American Chemical Society, Las Vegas, Nevada, August 1980. Also, for a communication on paniculide A, see: Smith, A. B.; Richmond, R. E. *J. Org. Chem.* **1981**, *46*, 4814.

(8) Paniculide C (**3**) has been prepared from paniculide B (**2**) via mild oxidation; see ref 1.

(9) After completion of this work, Overton reported the result of an X-ray crystallographic analysis of paniculide B that established the absolute configuration; see: Anastasis, P.; Freer, I.; Gilmore, C.; Mackie, H.; Overton, K.; Swanson, S. *J. Chem. Soc., Chem. Commun.* **1982**, 267.

(10) Henbest, H. B. *Proc. Chem. Soc., London* **1963**, *75*, 159. Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1374.

(11) For similar exploitation of a cyclobutanone ring as a latent γ-lactone, see Grieco's elegant total synthesis of ivangulin and eriolanin: (a) Grieco, P. A.; Oguri, T.; Wang, C. J.; Williams, E. *J. Org. Chem.* **1977**, *42*, 4113. (b) See ref 6.

(12) (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (b) Sharpless, K. B.; Lauer, R. F. *Ibid.* **1973**, *95*, 2697.

(13) (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (b) For selenium examples, see: Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542. Grieco, P. A.; Miyashita, M. *Ibid.* **1974**, *39*, 120.

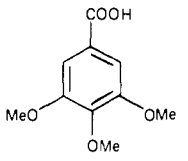
(14) For preparation of 1,1-diethoxyethylene, see: McElvain, S. M.; Kundiger, D. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 506.

In this regard, we could anticipate exclusive formation of a head-to-tail adduct, complicated only by the cis–trans nature of the ring fusion.[15] Fortunately for our purposes, the more strained trans isomer could be expected to convert conveniently and completely to the cis form via either base or thermal epimerization.[14]

At this point our strategies for paniculides A and B diverge. In the case of paniculide A, introduction of unsaturation was envisioned to exploit the Kochi–McMurry[16] lead tetraacetate oxidative-decarboxylation procedure. To this end, ketone **12** was designed to include the needed β-carboxyl functionality. For paniculide B we anticipated taking advantage of the Reich–Sharpless oxidative elimination or a related protocol.

(ii) Construction of Enones 12a and 13a: Substrates for Photochemical Cycloaddition. Our approach to enone **12a**, required for paniculide A, began with execution of a Birch reduction[17] on commercially available *m*-anisic acid employing lithium in liquid ammonia. In situ alkylation of the intermediate dianion[18] with methyl iodide, followed by evaporation of the ammonia, addition of 2 N HCl, and heating the resultant mixture at reflux for 0.5 h, afforded the desired enone acid **12b**[19a] in 94% yield. This three-step sequence was conveniently carried out as a one-pot procedure on a 30–40-g scale. Esterification employing methanolic *p*-toluenesulfonic acid then gave **12a**[18b] in 92% yield. For the record, all synthetic intermediates (vide infra) were fully characterized; for those not discussed in detail here, structural assignment rests on spectroscopic properties and elemental composition data on record in the Experimental Section.

Enone **13a**, on the other hand, was conveniently available via minor modification of the 1956 van Tamelen protocol.[20] Here, Birch reduction of 3,4,5-trimethoxybenzoic acid (**14**) with ethanol



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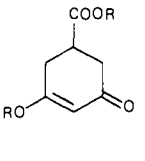
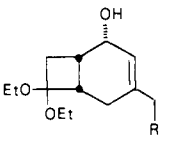


15a: R = H
b: R = Et

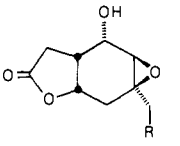
as the proton source led with concomitant reductive removal of the 4-methoxy group to acid **15a**. Esterification of both the carboxyl and vinylogous acid groups followed by $LiAlH_4$ reduction and acid hydrolysis then afforded 5-(hydroxymethyl)-2-cyclohexenone (**13b**). Interestingly, van Tamelen and Hildahl suggested that enone **13b** was not stable to purification; however, in our hands an analytical sample of **13b** could be prepared by flash chromatography. Finally, protection of the primary hydroxyl group as the *tert*-butyldimethylsilyl (TBDMS) derivative employing the Hernandez procedure[21] gave **13a**. The overall yield of **13a** on the basis of **14** was 51%. With ample quantities of substrates **12a** and **13a** available, we turned our attention toward the synthesis of paniculide A.

(iii) Synthesis of Advanced Intermediate 6a: Nucleus of Paniculide A. Taking advantage of the known propensity of enones to participate efficiently in [2 + 2] photochemical cycloaddition reactions, irradiation of **12a** in the presence of 3 equiv of diethoxyethylene afforded **9a** in 84% yield as a mixture of four diastereomers. This photochemical [2 + 2] cycloaddition was most conveniently carried out on a 15–20-g scale by employing the standard 450-W mercury arc fitted with a Pyrex filter. The resultant isomeric mixture was of little long-term consequence, in that saponification with 10% KOH effected complete epimerization to the more stable *cis*-bicyclo[4.2.0]octane system in 95% yield. Careful acidification (pH ~5) of the saponification reaction mixture was required to prevent hydrolysis of the ketal. Subsequent oxidative decarboxylation of the derived acid via the Kochi–McMurry lead tetraacetate protocol[16] then gave **8a** as a *single* compound in 40–45% yield after chromatography.

To set the stage for stereoselective introduction of the epoxide oxygen, it was necessary to reduce the enone carbonyl. Given the concave–convex nature of the bicyclo[4.2.0] system, either diisobutylaluminum hydride[22] or sodium borohydride in the presence of $CeCl_3$[23] was expected to lead to the α alcohol.[24] In the event, treatment with either reagent afforded a *single* allylic alcohol (i.e., **16a**). The yield in both cases was excellent, however workup of the $NaBH_4/CeCl_3$ reaction proved to be considerably more convenient.



16a: R = H
b: R = $OSiMe_2{}^tBu$

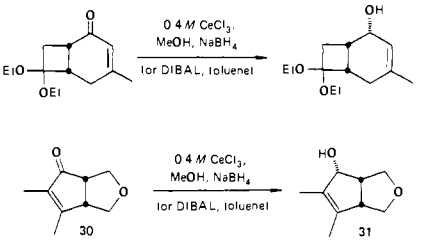


17a: R = H
b: R = $OSiMe_2{}^tBu$

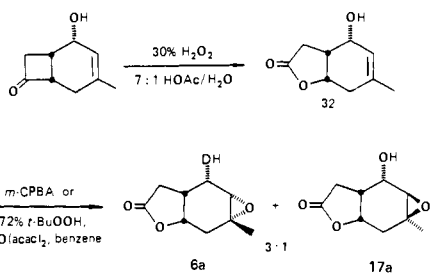
Deketalization of **16a** was then effected with acetic acid–tetrahydrofuran–water to give cyclobutanone **7a** (IR 1770 cm^{-1}). Oxidation of the latter with 3 equiv of *m*-CPBA in CH_2Cl_2 containing solid $NaHCO_3$ as buffer afforded a 3:1 mixture of epoxy lactones **6a** and **17a** in 84% yield. As anticipated, the major isomer **6a** (mp 135–136 °C) derived from C(8)-hydroxyl directed endo epoxidation (vide infra).[25]

(iv) Attachment of the Six-Carbon Side Chain: A Profitable Model Study. To assure that our strategy for the penultimate step was viable as well as to select the optimum electrophile, we ex-

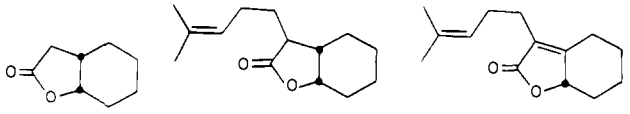
(15) Corey, E. J.; Bass, J.; LeMahieu, R.; Mitra, R. *J. Am. Chem. Soc.* **1964**, *86*, 5570.
(16) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2415. McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217.
(17) Birch, A. J.; Hextall, P.; Sternhell, S. *Aust. J. Chem.* **1954**, *7*, 256.
(18) For reductive Birch alkylation, see: (a) Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. E. *J. Org. Chem.* **1969**, *34*, 126. (b) Marshall, J. A.; Wuts, P. G. M. *Synth. Commun.* **1977**, *7*, 233.
(19) (a) For previous preparation of the enone acid **12b**, see: Kende, A. S.; Constantinides, D.; Lee, S. J.; Liebeskind, L. *Tetrahedron Lett.* **1975**, *6*, 405. (b) For previous preparation of enone ester **12a**, see: Banerjee, D. K.; Sarendranath, V. *Indian J. Chem.* **1975**, *13*, 201.
(20) van Tamelen, E.; Hildahl, G. T. *J. Am. Chem. Soc.* **1956**, *78*, 4405.
(21) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.
(22) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc. B* **1970**, 213.
(23) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. For an example exploiting the stereoselectivity of $NaBH_4$–Ce^{3+} protocol, see: Wender, P. A.; Lechleiter, J. C. *Ibid.* **1980**, *102*, 6340.
(24) To give further credence that the stereochemical outcome was as predicted, a similar bicyclic concave–convex system **30** was examined. Both



sodium borohydride–cerium chloride and diisobutylaluminum hydride gave a *single* isomer that was rigorously proven to be the α alcohol **31** by Scarborough and Smith via total synthesis to methylenomycin A (Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III *J. Am. Chem. Soc.* **1980**, *102*, 3904).
(25) An alternative route to **6a** and **17** was also achieved:



ecuted a model study with lactone **18**, prepared via the procedure

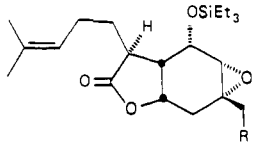


18 20 21

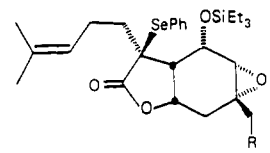
of Cope and Klein.[26] After several experiments, the electrophile of choice proved to be 2-methyl-5-iodo-2-pentene (**19**).[27] In particular, alkylation employing lithium diisopropylamide to generate the enolate proceeded smoothly at −78 °C to give **20** as the sole product. Stereochemical assignment of **20** was based on the expectation that electrophiles would approach the enolate of **18** from the β or convex face.[28]

Subsequent reaction of the lithium enolate derived from **20** (LDA in THF) with diphenyl diselenide in the presence of HMPA, afforded the corresponding α-phenylselenenyl derivative. Oxidative elimination employing the Sharpless–Reich conditions[12] then provided butenolide **21**. That the olefinic linkage possessed the desired endocyclic disposition was confirmed by spectral analysis; the high-field 250-MHz ^{1}H NMR spectra revealed a single olefinic multiplet at δ 5.04 as well as a discrete doublet of doublets at δ 4.55 (J = 5.1 Hz) for the hydrogen at the vinylic ring junction. Furthermore, the UV spectrum displayed a λ_{max} at 216 nm (EtOH, ϵ 8461). For comparison purposes, paniculide A and B exhibit λ_{max} at 216 (ϵ 15 500) and 217 nm (ϵ 17 000), respectively.

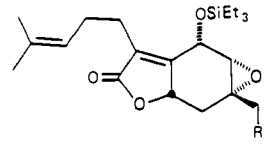
(v) Total Synthesis of Paniculide A: An Initial Solution. At this juncture we had in hand what appeared to be a viable strategy for both introduction of the side chain and unsaturation inherent to the butenolide ring of the paniculides. Initial studies however revealed that application of the model strategy to **6a** would first require protection of the C(8)-hydroxyl substituent. That is, all attempts to effect direct alkylation of **6a** lead only to complex mixtures. Examination of a number of protecting groups lead to selection of the triethylsilyl (TES) derivative[29] (i.e., **6c**), the latter most conveniently prepared in near-quantitative yield via the Hernandez procedure.[21] Subsequent alkylation with 2-methyl-5-iodopentene (**19**), in a manner identical with that employed in the model study, afforded **22a** in a 71% yield as a white



22a: R = H
b: R = $OSiMe_2{}^tBu$



23a: R = H
b: R = $OSiMe_2{}^tBu$



24a: R = H
b: R = $OSiMe_2{}^tBu$

crystalline solid (mp 60–61 °C). To our dismay, however, all attempts to employ lithium diisopropylamide in THF to effect deprotonation of **22a**, at a temperature commensurate with survival of the derived enolate, failed. It was only after a survey of a number of related lithium amide bases that we found that lithium tetramethylpiperidide (LiTMP), when employed under rather precise conditions, would effect the desired deprotonation. In particular, addition of **22a** to 1.2 equiv of LiTMP in THF, first at −10 °C for 1.5 h, then slow warming to 0 °C over a period of 30 min, recooling to −20 °C, and addition of phenyl selenenyl chloride (2 equiv) in THF–HMPA (8:1), led to the desired selenide **23a** as a crystalline solid (mp 128–130 °C). The yield, on the basis of recovered starting material, was 49%.

Oxidative elimination of the selenenyl group followed by removal of the TES protecting group were now all that remained to complete the synthesis of paniculide A. Fortuitously, our initial conditions, excess sodium metaperiodate in THF–H_2O, were sufficiently acidic to effect simultaneous removal of the TES group. The result was racemic paniculide A in 72% yield. Purification via thin-layer chromatography afforded an analytical sample as a white crystalline solid (mp 99–100 °C). That indeed paniculide A was in hand was demonstrated by careful spectroscopic and chromatographic comparisons with that of an authentic sample of paniculide A generously provided by Professor Overton.[30]

Oxidative elimination of **23a** without loss of the C(8) protecting group could also be achieved via exposure for 1.5 h to 15% H_2O_2 in CH_2Cl_2 containing 4.0 equiv of pyridine to destroy any phenylselenenic acid. Subsequent removal of the protecting group could then be achieved with acetic acid–tetrahydrofuran–water to give (±)-paniculide A in 95% yield. Although this sequence is one step longer, the overall yield was better (81% compared to 72%).

(vi) Total Synthesis of Paniculide B. Having completed the paniculide A venture, we anticipated construction of paniculide B, a simple C(15)-hydroxyl derivative of paniculide A, to be rather straightforward. This premise appeared especially true given the already described availability of enone **13a**. The only significant difference between the two strategies, after all, concerned the method of introduction of unsaturation into the six-membered ring of the initial photoadduct.

As in the paniculide A synthesis, we initiated the approach with the [2 + 2] photocycloaddition of enone **13a** to 1,1-diethoxyethylene. The resultant adduct, again a mixture of four head-to-tail diastereomers (**9b**), was produced in 90% yield. No attempt to separate the mixture was made since in the end introduction of unsaturation at C(9,10) and epimerization to the more stable *cis*-bicyclo[4.2.0]octane system would lead to a single compound (i.e., **8b**).

To our dismay, however, all efforts to introduce the required unsaturation either directly via the Reich–Sharpless procedure[12] or by other conventional oxidation protocols was unsucessful. The problem appeared to reside in the elimination step, since it was possible to prepare the lithium enolate of **9b** with LiTMP and to capture the latter as the enol silyl ether (vide infra). Presumably, the simultaneous trigonalization of two sp^3 centers in the already strained bicyclo[4.2.0]octane system precluded conventional ketone to enone interconversions.[31] Interestingly, epimerization of the trans diastereomers to the cis systems (i.e., 4% KOH in 1:1 MeOH–H_2O) to lessen the ring strain, while successful, did not improve the situation.

To circumvent the problem, we took advantage of the Saegusa method (i.e., palladium(II)-catalyzed dehydrosilylation).[32] Enol silyl ether **25**, prepared at −20 °C by deprotonation of ketone **9b** with LiTMP in THF followed by addition of 5 equiv of trimethylsilyl chloride, was immediately exposed to palladium acetate (0.5 equiv) and *p*-benzoquinone (0.5 equiv) in anhydrous aceto-

(26) For preparation of cis-lactone **18**, see: (a) Cope, A. C.; D'Addieco, A. A.; Whyte, D. E.; Glickman, S. A. "Organic Syntheses"; Wiley: New York, 1960; Collect. Vol. IV, p 234. (b) Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611.

(27) The homoallylic iodide was prepared via a modification of the Julia procedure. For details, see: Biernacki, W.; Gdula, A. *Synthesis* **1979**, *1*, 37.

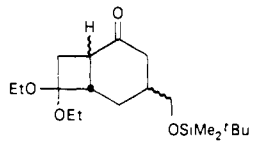
(28) For previous use of homoallylic iodide **19** as an electrophile in the alkylation of a lactone, see: Marshall, J. A.; Wuts, P. G. M. *J. Am. Chem. Soc.* **1978**, *100*, 1627.

(29) Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156.

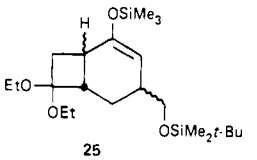
(30) We thank Professor Karl H. Overton of the University of Glasgow for providing very generous samples of paniculides A and B as well as for copies of spectral data on all three paniculides (i.e., ^{1}H and ^{13}C NMR).

(31) Contemporary with our results, Wender employed the same rationale and procedure to introduce a double bond into a system not dissimilar to our system; see: Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 6340. We thank Professor Wender for helpful discussions on this matter.

(32) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.



9b



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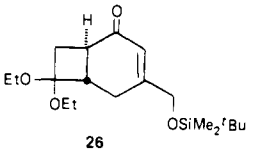


26

nitrile. The result was a 2:1 mixture of diastereomers at the cyclobutane ring junction. For characterizational purposes, these isomers (**26** and **8b**) could be separated by flash chromatography; the major isomer was shown to possess the trans ring junction by equilibration to the more stable cis isomer (**8b**). Interestingly, this epimerization process was found to proceed under milder conditions (2% KOH in 1:1 MeOH–H_2O) than the corresponding saturated system (i.e., **9b**) although some loss of the TBDMS protecting group was observed in both cases. Epimerization of **26** could also be accomplished in near-quantitative yield by impregnating neutral alumina with an etheral solution of the enone mixture (30 min); under these conditions no loss of the protecting group was observed. Thus in practice, the Saegusa protocol was employed directly on the diastereomeric mixture of photoadducts followed by neutral alumina promoted equilibration. The overall yield of **8b** from enone **13a** via this sequence was 37%.

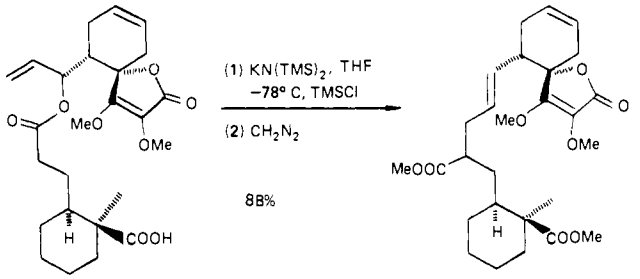
Spectroscopically, **26** and **8b** were readily distinguishable via their high-field 250-MHz ^1H NMR spectra; in the cis isomer the ketal methyl groups were observed as two distinct triplets at δ 1.14 (J = 7.30 Hz) and δ 1.24 (J = 6.80 Hz) while in the trans isomer the two triplets overlap at δ 1.25 to give an apparent quartet. Furthermore, in the cis isomer (**8b**), the bridgehead protons H_a and H_b, respectively, appear at δ 2.83 (apparent sextet) and at δ 3.11 (apparent triplet, J = 9.4 Hz); both were downfield relative to the bridgehead protons of the trans isomer that display as a complex multiplet (δ 2.16–2.70).

With a successful procedure for introduction of unsaturation into the six-membered ring of **9b** available, the remainder of the paniculide B approach was designed to parallel directly that of paniculide A. Toward this end, reduction of enone **8b** with sodium borohydride–cerium(III) chloride afforded endo alcohol **16b** in 86% yield, again as a single product. Subsequent deketalization in anticipation of the Baeyer–Villiger epoxidation sequence could not be accomplished by selectively employing the previously utilized acetic acid–tetrahydrofuran–water conditions due to simultaneous loss of the TBDMS group. Instead, transketalization[33] employing 0.3 equiv of pyridium *p*-toluenesulfonate at the reflux point of 2-butanone led cleanly and in high yield (81%) to **7b**. The resultant cyclobutanone (**7b**), isolated as a crystalline solid (mp 87–88 °C), was then subjected to Baeyer–Villiger epoxidation (3 equiv of *m*-CPBA) to give a mixture of epoxides **6b** and **17b**. Noteworthy here, the same 3:1 ratio of β to α epoxide was obtained as in the paniculide A synthesis. The desired, more polar epoxy lactone **6b** (mp 87–88 °C) could be readily separated from the minor isomer via flash chromatography. Subsequent protection of the secondary hydroxyl with triethylsilyl chloride followed by alkylation with 2-methyl-5-iodo-2-pentene (**19**) proceeded as anticipated to afford **22b** (mp 45–46 °C) in 72% yield. As with paniculide A and the model system, the alkylation proceeded with high stereoselectivity.

Confident that LiTMP, utilized to great advantage in the paniculide A approach, would again effect deprotonation of **22b**, we proceeded without hesitation to the selenenylation step. Unfortunately, all attempts to generate the requisite enolate, irrespective of the lithium amide base, resulted only in recovered starting material.

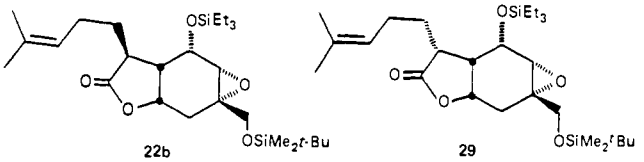
Undaunted by lack of initial success, we reexamined with some care the differences between lactones **22a**, **22b**, and model **18**. Recall that the model system was alkylated and selenenylated without event by employing lithium diisopropylamide as the base. In the case of paniculide A (i.e., lactone **22a**), the side chain was appended through aegis of lithium diisopropylamide; selenenylation on the other hand could only be effected with a somewhat stronger base, lithium tetramethylpiperidide.[34] In the paniculide B series, even lithium tetramethylpiperidide would not effect the required deprotonation.

From the steric point of view, the C(6) α-hydrogens in both **22a** and **22b** appeared equally encumbered. In fact, the only obvious difference between the two series was that **22b** possessed an additional hydroxyl substituent at C(15), the latter protected as the *tert*-butyldimethylsilyl ether. Put more simply, the only substantial differences between the two paniculide substrates and the model system concerned the number and locus of oxygen atoms. This difference led us to conjecture that a strong lithium–oxygen coordination might prohibit deprotonation of the C(6)-hydrogen by blocking approach of the amide base. Such an effect is not without precedent. Ireland,[35] in attempting to effect deprotonation of **27**, an intermediate in his chlorotricolide synthesis, found that lithium amide bases were unsuccessful. He attributed this effect to lithium coordination with the ether oxygen of the tetronic acid; this in turn prevented approach of the amide base to the proprionate side chain. Interestingly, lithium amide bases had proven quite effective in his earlier model studies.[36] The latter, of course, were considerably less oxygenated. By employing the more highly dissociated base, potassium bis(trimethylsilyl)-amide $KN(SiMe_3)_2$[37] Ireland was able to effect the desired deprotonation and subsequent rearrangement (**27** → **28**).



27 **28**

With this information in mind, lactone **22b** was treated with 3 equiv of potassium bis(trimethylsilyl)amide at −100 °C for 10 min, followed by addition of diphenyl diselenide (5 equiv) and hexamethylphosphoramide (3 equiv). After slow warming to −20 °C, the reaction was quenched with brine. While selenenylation was not observed, two promising results were observed. First, we could be assured that deprotonation had occurred since two compounds, one of which proved to be starting material (**22b**), and the other its C(6) epimer (**29**), were isolated. The ratio was



22b **29**

approximately 1:1. Second, if the reaction was monitored by thin-layer chromatography, a new UV-active substance could be detected after addition of diphenyl diselenide. Upon workup, however, only starting material and its epimer were isolated. We

(33) (a) For the preparation of PPTS, see: Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772. (b) For the cleavage of acetals, see: Sterzycki, R. *Synthesis* **1979**, 724.

(34) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.
(35) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.
(36) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(37) Brown, C. A. *J. Org. Chem.* **1972**, *39*, 3913.

conjectured that the new UV-active material was in fact the desired selenenylated lactone (i.e., **23b**). However, in the presence of the phenylselenenyl anion, produced as a byproduct of the selenenylation process, **23b** was deselenenylated during the room-temperature workup. Interestingly in this regard, Reich[12] demonstrated that diphenyl diselenide does not react with lithium enolates derived from ketones due to an unfavorable equilibrium. This result is not a kinetic barrier to selenenylation but rather an equilibrium effect. In our system $PhSe^-K^+$ was the likely culprit. We reasoned that if this anion could be removed from the reaction coordinate, the equilibrium would shift toward selenenylation and thereby circumvent the problem. Realizing that it might be possible to remove the phenylselenenyl anion by oxidation,[38] oxygen was passed directly into the cold reaction mixture for 1 h prior to workup. To our delight, the desired selenide **23b** was isolated as a white crystalline solid (mp 97–98 °C) in 82% yield based on recovered starting material.

With successful selenenylation conditions established, oxidative elimination of the phenylselenenyl group followed by removal of the two protecting groups would lead to paniculide B. Interestingly, unlike the elimination process in the paniculide A series, selenoxide **23b** required heating for 2–3 h at the reflux point of methylene chloride to effect complete elimination. Subsequent liberation of both protecting groups (acetic acid–tetrahydrofuran–water) afforded racemic paniculide B (**2**) as a white crystalline solid, mp 126–127 °C. The identity of synthetic (±)-paniculide B was confirmed by careful comparison of the high-field (250 MHz) ^1H and (62.9 MHz) ^{13}C NMR, IR, and mass spectroscopic properties as well as TLC mobility (two-solvent systems) with that of an authentic sample of paniculide B again generously provided by Professor Overton.

(vii) Return to the Paniculide A Synthesis: Application of the Modified Selenenylation Procedure. The discovery that selenenylation of **22b** was most effectively carried out with potassium bis(trimethylsilyl)amide as base and diphenyl diselenide as the electrophile, in conjunction with oxygen treatment prior to workup, suggested that a significant improvement in the paniculide A synthesis might be possible. Indeed, application of this protocol to **22a** led to a much improved yield of the corresponding selenide (i.e., 72%). This result in turn increased the overall yield of paniculide A from 4.2 to 5.5%.

(viii) Synthesis of Paniculides C and D. Since Overton and co-workers[1] had transformed paniculide B to paniculide C during their characterization studies, our synthesis of paniculide B constituted a formal total synthesis of paniculide C (**3**). However, for the sake of completeness as well as for spectral comparison, we prepared racemic paniculide C via oxidation of B with 5 equiv of manganese dioxide[39] in methylene chloride. A 64% yield of paniculide C resulted. The yield of purified paniculide C however was somewhat variable due to its instability toward silica gel chromatography. This instability was previously noted by Butcher and Connolly during their biosynthetic studies.

The presence of paniculide C in culture filtrates of *Andrographis paniculata* suggested that the corresponding oxo analogue derived from paniculide A, which we term paniculide D (**4**), might prove to be a natural product. With the idea of supplying paniculide D to the Glascow group in order that they might examine the culture filtrates of *A. paniculata* for its presence, we subjected paniculide A to pyridinium chlorochromate oxidation.[40] Paniculide D was obtained in 68% yield. Confirmation of the structure was secured through careful comparison of its spectroscopic properties to those obtained for paniculide C. Interestingly, like paniculide C, paniculide D was also somewhat unstable to silica gel chromatography. Indeed, storage at 0 °C was required to maintain the sample.

(ix) Summary. The first total synthesis of paniculides A–D, via a common synthetic route, has been achieved in a highly stereocontrolled fashion. The approach proved to be both economical and quite efficient (5.5% for paniculide A and 3.6% for paniculide B). Perhaps the only disappointing observation was the fact that the epoxidation sequence was stereoselective only to the extent of 3:1. From the synthetic point of view, two potentially useful observations emanated from the paniculide venture. First, potassium amide bases [i.e., $KN(SiMe_3)_2$] prove more effective in the deprotonation of highly oxygenated systems than the corresponding lithium bases. Second, the utility of diphenyl diselenide as an electrophile can be greatly improved simply by oxidation of the selenenylation reaction mixture prior to workup.

(38) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.
(39) Evans, R. M. *Q. Rev., Chem. Soc.* **1959**, *13*, 61.
(40) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399.

Experimental Section

Materials and Methods. Melting points were taken on a Thomas-Hoover capillary melting apparatus and are corrected. Boiling points are uncorrected. All solvents were reagent grade and were distilled prior to use: benzene and toluene from sodium, ether and THF from sodium and benzophone, DMF from calcium hydride, ethylene glycol from magnesium sulfate, HMPA from CaH, and Me_2SO from molecular sieves. Unless otherwise specified, solutions were dried over $MgSO_4$. IR spectra were obtained for CCl_4 solutions on a Perkin-Elmer Model 337 spectrophotometer. ^1H NMR spectra were obtained in the indicated solvent on either a Varian Model A-60 (60 MHz) or T-60A (60 MHz), Bruker WP-250 FT (250 MHz), or a Bruker WH-360 (360 MHz) spectrophotometer. Carbon NMR spectra were recorded on a Bruker WP-250 at 62.9 MHz. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane, (δ Me_4Si = 0.00 ppm) and coupling constants are reported in hertz (Hz). High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi-Perkin-Elmer RMH-2 high-resolution double-focusing electron impact spectrometer or a V. G micromass 70/70 H high-resolution double-focusing electron impact–chemical ionization spectrometer, the latter using isobutene as the reagent gas, and each interfaced with a Kratos DS-50-S data system. Precoated silica gel plates (250 μm) with a fluorescent indicator (E. M. Merck) were used for analytical thin-layer chromatography (TLC). Preparative separations were performed on precoated silica gel GF (Analtech) plates (250, 500, or 1000 μm). Visualization was achieved either under ultraviolet light or with ethanolic 12-molybdophosphoric acid [7% (w/v)]. Silica gel 60 (particle size 0.040–0.063 mm) supplied by E. M. Merck was employed for flash chromatography and medium-pressure liquid chromatography.

1-Methyl-5-oxo-3-cyclohexenecarboxylic Acid (12b).[19] To a stirring solution of *m*-anisic acid (30 g, 0.20 mol) in 200 mL of anhydrous tetrahydrofuran and 1 L of ammonia was added lithium wire (5.48 g, 0.79 mol, 4 equiv) until the blue color persisted. The reaction was stirred at −78 °C for 1 h. A solution of methyl iodide (36 mL, 0.28 mol) in 30 mL of tetrahydrofuran was added rapidly. At this point, the reaction mixture turned from blue to colorless. After stirring for an additional 1.5 h, the reaction was quenched with solid ammonium chloride, and the ammonia was evaporated under a stream of nitrogen. The residue was acidified with 2 N hydrochloric acid and then heated to reflux for 20 min. After cooling, the solution was thoroughly extracted with ether and dried. Removal of the solvent in vacuo gave an oil that solidified upon standing (29.21 g, 96%). Recrystallization from a benzene–hexane mixture afforded unsaturated acid **12b** (mp 85–86 °C): IR ($CHCl_3$) 3650 (w, sh), 2400–3600 (s, br), 1720 (s), 1685 (s), 1620 (m), 1455 (m), 1470 (s), 1130 (m), 940 (w), 905 (s), 835 (w), 600 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 2.35 (d, J = 14.4 Hz, 2 H), 2.82–3.06 (m, 2 H), 6.02 (d, J = 10.8 Hz, 1 H), 6.85–7.0 (m, 1 H), 11.46 (br s, 1 H); electron impact mass spectrum, m/e 154.0640 (M^+), calcd for $C_8H_{10}O_3$, 154.0630.

Methyl 1-Methyl-5-oxo-3-cyclohexenecarboxylate (12a).[19] To a solution of enone **12b** (13.27 g, 86.2 mmol) in 560 mL of benzene and 112 mL of methanol was added a catalytic amount of *p*-toluenesulfonic acid (0.63 g, 3.31 mmol). The reaction mixture was heated at reflux for 18 h with water separation (Dean–Stark trap). After cooling to room temperature, the reaction mixture was filtered and then washed with saturated aqueous sodium bicarbonate and brine, followed by drying. Removal of the solvent in vacuo and Kugelrohr distillation (1 mmHg, 115–117 °C) afforded 11.59 g (80.1%) of methyl ester **12a** as a colorless viscous oil: IR (CCl_4) 3040 (m), 2850–3000 (m), 1730 (s), 1680 (s), 1610 (w), 1475 (m), 1400 (m), 1320 (m), 1215 (s), 1130 (m), 1110 (m), 990 (m), 905 (m), 835 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.38 (s, 3 H), 2.26–2.44 (m, 2 H), 2.82–2.98 (m, 2 H), 3.70 (s, 3 H), 6.0 (dt, J = 2.1, 10.9 Hz, 1 H), 6.80–6.92 (m, 1 H); electron impact mass spectrum, m/e 168.0789 (M^+), calcd for $C_9H_{12}O_3$, 168.0786.

3-Ethoxy-5-carbethoxy-2-cyclohexenone (15b).[20] To a cooled solution of (−78 °C) 3,4,5-trimethoxybenzoic acid (**14**) (10.77 g, 50.8 mmol) in 75 mL of absolute ethanol was added 400 mL of freshly distilled anhydrous liquid ammonia. Small pieces of sodium metal (6 g) were added

until the solution remained dark blue for 5 min. The reaction mixture was stirred at −78 °C for an additional 45 min. Excess sodium was then quenched by the addition of solid ammonium chloride (25 g), and the ammonia was allowed to evaporate overnight under a stream of nitrogen. The mixture was acidified with 150 mL of 2 N hydrochloric acid (pH 2). An additional 50 mL of ethanol was added, and the resultant mixture was heated at reflux for 20 min. After cooling, the reaction mixture was extracted with ethyl acetate, dried, and the solvent evaporated *in vacuo* to yield 10.47 g of a yellow residue, which was shown by NMR to be a mixture of **15b** and **15a**. The olefinic region δ 5.32 and 5.26 (s, s, 0.2 H, 0.8 H) indicated a 4:1 mixture of **15b** and **15a**, respectively.

In practice, the mixture was esterified without separation or purification. However, acid **15a** could be purified for analytical purposes by pouring the mixture into 10% sodium hydroxide and extracting with ether. The aqueous phase was acidified with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was dried, concentrated in vacuo, and the resulting solid recrystallized from ethyl acetate to afford a white crystalline solid: mp 183–184 °C (lit.[17] mp 180 °C); IR (Nujol) 2150–3800 (s, br), 1685 (s), 1550 (s), 1330 (s), 1270 (m), 1240 (m), 1210 (m), 1135 (m), 825 (m), 670 (m) cm^{-1}; ^1H NMR (60 MHz, Me_2SO-d_6) δ 2.30–2.70 (m, 5 H), 2.70–3.32 (m, 1 H), 5.15 (s, 1 H), 11.17 (br s, 1 H).

To a solution of the above mixture (**15a** and **15b**) in 150 mL of benzene and 30 mL of absolute ethanol was added a catalytic amount (300 mg, 1.58 mmol) of *p*-toluenesulfonic acid. The reaction mixture was heated at reflux for 48 h with water separation (Dean–Stark trap). The solution was cooled, filtered, and washed with saturated aqueous sodium bicarbonate and brine, followed by drying. Removal of the solvent in vacuo and Kugelrohr distillation (0.5 mmHg, 125–126 °C) afforded 7.10 g of **15b** (66% from 3,4,5-trimethoxybenzoic acid) as a viscous colorless oil, which solidified upon standing at 4 °C: IR ($CHCl_3$) 2900–3100 (m), 1730 (s), 1660 (s), 1615 (s), 1380 (m), 1355 (m), 1240 (s, br), 1040 (m), 945 (w), 810 (w), 710 (m), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (t, J = 8.3 Hz, 3 H), 1.43 (t, J = 7.3 Hz, 3 H), 2.47–2.83 (complex m, 4 H), 3.07 (apparent heptet, J = 8.9, 7.3, 6.3, 7.3 Hz, 1 H), 3.95 (q, J = 8.3 Hz, 2 H), 4.19 (q, J = 7.3 Hz, 2 H), 5.37 (s, 1 H); electron impact mass spectrum, m/e 212.1032 (M^+), calcd for $C_{11}H_{16}O_4$, 212.1049.

5-(Hydroxymethyl)-2-cyclohexen-1-one (13b).[20] To a suspension of lithium aluminum hydride (374 mg, 10 mmol) in 50 mL of ether was added ester **15b** (2.09 g, 10 mmol) in 10 mL of ether in a dropwise fashion. The solution was stirred at 25 °C for 1.5 h; the excess lithium aluminum hydride was destroyed by adding $Na_2SO_4 \cdot 10H_2O$ until gas was no longer evolved. The alumina salts were removed by filtration, and the solvent was concentrated in vacuo to afford an oily residue.

Without purification, the unstable enol (1.61 g) was dissolved in 5 mL of tetrahydrofuran and 5 mL of 10% acetic acid followed by stirring for 3 h. The reaction mixture was poured into ether, washed with brine, dried, and concentrated in vacuo. Any residual acetic acid was removed via azeotrope with heptane. The enone (**13b**) was afforded as a pale yellow oil in 89% from ester **15b** (1.10 g): IR ($CHCl_3$) 3630 (m, sh), 3300–3350 (m, br), 2850–3050 (m), 1660 (s), 1450 (w), 1380 (s), 1250 (s), 1170 (w), 1140 (w), 1080 (s), 1030 (m), 960 (w), 900 (w), 875 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.94–2.54 (complex m, 6 H), 3.51–3.82 (m, 2 H), 6.01 (d, J = 9.9 Hz, 1 H), 6.95–7.01 (m, 1 H); electron impact mass spectrum, m/e 126.0672 (M^+), calcd for $C_7H_{10}O_2$, 126.0681.

5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-cyclohexen-1-one (13a). A mixture of *tert*-butyldimethylsilyl chloride (4.22 g, 28 mmol), triethylamine (4.68 mL, 46 mmol), and a catalytic amount of dimethylaminopyridine (137 mg, 0.04 equiv) were stirred in 30 mL of dry methylene chloride for 10 min. To this mixture was added a solution of enone **13b** (3.53 g, 28 mmol) in 5 mL of methylene chloride. The reaction was stirred overnight at 25 °C under an argon atmosphere. The mixture was diluted with methylene chloride, washed with saturated ammonium chloride, water, and brine, and dried. Removal of the solvent in vacuo and Kugelrohr distillation (0.1 mmHg, bp 120–121 °C) afforded **13a** (5.88 g, 87%) as a colorless oil: IR (CCl_4) 2860–3040 (s), 1680 (s), 1620 (w), 1460 (m), 1385 (m), 1260 (s), 1110 (s, br), 960 (m), 825 (s), 650 (m), 600 (w, br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.10 (s, 6 H), 0.95 (s, 9 H), 2.20–2.54 (m, 5 H), 3.51–3.65 (m, 2 H), 6.02 (d, J = 9.7 Hz, 1 H), 6.98 (apparent octet, J = 2.6, 9.7, 2.6, 3.7 Hz, 1 H); chemical ionization mass spectrum, m/e 241.1619 (MH^+), calcd for $C_{13}H_{25}O_2Si$, 241.1623.

Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.89; H, 10.18.

Methyl 8,8-Diethoxy-3-methyl-5-oxobicyclo[4.2.0]octane-3-carboxylate (9a). A solution of methyl ester **12a** (13.17 g, 0.078 mol), 1,1-diethoxyethylene (20.88 g, 0.18 mol), and 235 mL of anhydrous benzene was purged under a nitrogen atmosphere for 20 min and then irradiated through a Pyrex filter for 5 h. The reaction was monitored by thin-layer chromatography [50:50 ether–hexane (v/v)]. The solvent was evaporated in vacuo, and excess 1,1-diethoxyethylene was removed via distillation through a short Vigreux column. Kugelrohr distillation (1 mmHg, 130–160 °C) afforded **9a** as a mixture of diasteriomers (18.62 g, 84%), which were not separated: IR ($CHCl_3$) 2975 (s), 2940 (m), 2880 (m), 1710 (s), 1475 (m), 1435 (m), 1400 (m), 1320 (m), 1240 (s), 1050 (s), 950 (m), 900 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16–1.54 (complex m, 10 H), 1.78–3.02 (complex m, 7 H), 3.34–3.62 (m, 4 H), 3.66–3.80 (m, 3 H); electron impact mass spectrum, m/e 284.1640 (M^+), calcd for $C_{15}H_{24}O_5$, 284.1624.

8,8-Diethoxy-3-methyl-5-oxobicyclo[4.2.0]octane-3-carboxylic Acid. To a solution of ester **9a** (6.21 g, 21.8 mmol) in 85 mL of methanol was added 85 mL of 10% aqueous potassium hydroxide. The reaction mixture was stirred under a nitrogen atmosphere for 12 h. The basic solution was extracted with ether to remove impurities, and then the aqueous phase was carefully acidified to pH 5 and then extracted thoroughly with ether. After the organic extracts were dried, removal of solvent in vacuo afforded an isomeric mixture of acids (5.59 g, 95%): IR (CCl_4) 2600–3600 (m, br), 1700 (s), 1450 (w), 1400 (w), 1180 (m), 1130 (m), 1060 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) 1.18–1.28 (m, 6 H), 1.34 (s, 3 H), 1.84–2.96 (m, 8 H), 3.08–3.54 (m, 4 H);[41] chemical ionization mass spectrum, m/e 271.1561 (MH^+), calcd for $C_{14}H_{23}O_5$, 271.1546.

***cis*-7,7-Diethoxy-4-methylbicyclo[4.2.0]oct-3-en-2-one (8a).** A solution of the above acid (1.03 g, 3.82 mmol), cupric acetate (200 mg, 1.0 mmol), 1.15 mL of pyridine, and 30 mL of benzene were stirred at room temperature under nitrogen until the mixture became a homogeneous green solution. Oxygen and light were rigorously excluded from the reaction mixture. Lead tetraacetate (5.02 g, 11.3 mmol, 3 equiv) was added, and the reaction mixture was stirred in the dark for 3 h. The reaction mixture was brought to reflux for 1 h, at which time vigorous gas evolution occurred. After cooling, the mixture was passed through a pad of neutral alumina to remove inorganic residue and eluted with ether. The organic filtrate was washed with water, saturated ammonium chloride, and saturated sodium bicarbonate and dried. Following concentration in vacuo, flash chromatography on silica gel [40:60 ether–hexane (v/v)] yielded 361 mg (43%) of enone **8a**: IR (CCl_4) 2875–3040 (s), 1660 (s), 1475 (s), 1445 (m), 1405 (m), 1310 (m), 1250 (m), 1140 (m), 1040 (s), 930 (w), 880 (w), 840 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (t, J = 7.1 Hz, 3 H), 1.18 (t, J = 7.1 Hz, 3 H), 1.94 (s, 3 H), 2.20–2.42 (m, 2 H), 2.45–2.60 (m, 2 H), 2.72 (apparent sextet, J = 4.63, 9.25, 9.25 Hz, 1 H), 3.06 (bt, J = 9.25 Hz, 1 H), 3.28–3.58 (m, 4 H), 5.88 (br s, 1 H); electron impact mass spectrum, m/e 224.1416 (M^+), calcd for $C_{13}H_{20}O_3$, 224.1412.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.54; H, 8.78.

(1α,2β,6α)-7,7-Diethoxy-4-methylbicyclo[4.2.0]oct-3-en-2-ol (16a). Enone **8a** (902 mg, 4.02 mmol) was dissolved in 10.1 mL of a cerium(III) chloride solution (0.4 M $CeCl_3$) in methanol. The reaction mixture was cooled to 0 °C, and sodium borohydride (159 mg, 4.18 mmol) was added slowly. The mixture was allowed to stir for 10 min, followed by the addition of water to destroy excess sodium borohydride. The solution was extracted with ether, washed with brine, and dried. Removal of solvent in vacuo afforded 815 mg (90%) of **16a** as a pale yellow oil: IR (CCl_4) 3630 (w, br), 3250–3600 (m, br), 2800–3060 (s), 1480 (m), 1440 (m), 1250 (m), 1190 (m), 1140 (m), 1100 (m), 1050 (m), 1000 (m), 940 (m), 905 (m), 840 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3 H), 1.18 (t, J = 7.2 Hz, 3 H), 1.76 (s, 3 H), 1.75–1.93 (m, 3 H), 1.99–2.13 (m, 2 H), 2.60 (q, J = 7.6 Hz, 1 H), 2.72 (q, J = 7.6 Hz, 1 H), 3.34 (q, J = 7.2 Hz, 2 H), 3.40 (q, J = 7.2 Hz, 2 H), 4.21–4.28 (m, 1 H), 5.18 (br s, 1 H); electron impact mass spectrum, m/e 226.1543 (M^+), calcd for $C_{13}H_{22}O_3$, 226.1569.

Alternative Preparation of Allylic Alcohol 16a. A solution of enone **8a** (61 mg, 0.27 mmol) in 3 mL of toluene cooled to 0 °C was treated dropwise with 1.5 equiv of diisobutylaluminum hydride (411 μL, 1 M in hexane). After 3 h at 0 °C, the reaction was quenched via addition of 2 mL of methanol, followed by warming to room temperature. The reaction was stirred for an additional hour. The workup consisted of filtration of the resultant salts and removal of solvent in vacuo. Purification by preparative thin-layer chromatography (PLC) (1000 μm, 7:1 ether–hexane) afforded 38 mg (62%) of a single isomer as a colorless oil. The compound was identical in all respects with allylic alcohol **16a** prepared previously.

Preparation of Allylic Alcohol 31.[24] Enone **30** (34 mg, 0.22 mmol) was dissolved in 1 mL of 0.4 M methanolic cerium(III) chloride solution that was cooled to 0 °C. Sodium borohydride (10 mg, 0.26 mmol) was added slowly. The mixture was allowed to stir for 10 min followed by

(41) The hydroxyl hydrogen of the carboxylic acid was too broad for observation.

addition of water to destroy excess sodium borohydride. The solution was extracted into ether, washed with brine, and dried. Removal of solvent in vacuo afforded 32 mg (93%) of allylic alcohol **31**, which was identical, via NMR and IR, with a sample previously prepared by Scarborough[24] via reduction with diisobutylaluminum hydride.

(1α,2β,6α)-2-Hydroxy-4-methylbicyclo[4.2.0]oct-3-en-7-one (7a). A mixture of bicyclo ketal **16a** (905 mg, 4.04 mmol), 9 mL of acetic acid, 6 mL of water, and 6 mL of tetrahydrofuran was stirred under nitrogen for 0.5 h. The reaction mixture was poured into ether, washed with water and brine, and dried over anhydrous potassium carbonate. After concentration in vacuo, residual acetic acid was removed via an ether–heptane azeotrope. This afforded 615 mg (99%) of colorless oil **7a**, which was carried on to the next step without purification. An analytical sample was obtained via flash chromatography on silica gel [40:60 ether–hexane (v/v)]: IR (CCl_4) 3640 (w, sh), 3200–3600 (m, br), 2855–3045 (s), 1770 (s), 1650 (m), 1450 (m), 1435 (m), 1250 (m), 1100 (m), 1075 (m), 1060 (m), 690 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.72 (s, 3 H), 1.90 (br s, 1 H), 2.02–2.14 (m, 1 H), 2.24 (d, J = 15.0 Hz, 1 H), 2.84–3.14 (m, 3 H), 3.46–3.60 (m, 1 H), 4.65 (br s, 1 H), 5.48 (s, 1 H); electron impact mass spectrum, m/e 152.0812 (M^+), calcd for $C_9H_{12}O_2$, 152.0837.

Preparation of Epoxy Lactones 6a and 17a. To a solution of allylic alcohol **7a** (541 mg, 3.56 mmol) in 10 mL of dry methylene chloride containing suspended sodium bicarbonate (972 mg, 11.57 mmol) at 0 °C was added *m*-chloroperoxybenzoic acid (2.13 g, 10.29 mmol). This solution was allowed to stand at 5 °C for approximately 15 h. Anhydrous potassium carbonate was added, and the mixture was stirred for 45 min. This solution was then filtered to remove the precipitated salt. After removal of the solvent in vacuo, purification of the resultant mixture by silica gel flash chromatography employing 4:1 ethyl acetate–ether (v/v) afforded epoxy lactones **6a** and **17a**, 3:1, respectively.

The major isomer **6a** was isolated as a white crystalline solid (mp 135–136 °C) in a 64% yield (420 mg, R_f 0.19): IR (Nujol) 3390–3560 (m), 2810–3000 (s), 1760 (s), 1475 (m), 1430 (m), 1210 (m), 1085 (m), 1065 (m), 1010 (m), 910 (m), 880 (m), 860 (m), 830 (m) cm^{-1}; ^1H NMR (360 MHz, acetone-d_6) δ 1.31 (s, 3 H), 1.91–1.99 (m, 1 H), 2.14 (d, J = 7.2 Hz, 2 H), 2.36 (dd, J = 10.8, 18.0 Hz, 1 H), 2.84 (dd, J = 5.4, 18.0 Hz, 1 H), 2.94–3.06 (m, 2 H), 4.31 (d, J = 7.2 Hz, 1 H), 4.58–4.68 (m, 1 H).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.67; H, 6.57. Found: C, 58.38; H, 6.42.

The minor isomer, epoxy lactone **17a** was isolated in 22% yield (128 mg, R_f 0.42): IR ($CHCl_3$) 3675 (s), 3450 (b), 2940 (s), 1760 (s), 1440 (m), 1160 (m), 1065 (m), 1000 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 3 H), 2.27 (dd, J = 7.5, 15.0 Hz, 1 H), 2.48–2.72 (complex, m, 5 H), 3.20 (d, J = 5.0 Hz, 1 H), 4.33 (br s, 1 H), 4.64–4.76 (m, 1 H); chemical ionization mass spectrum, m/e 185.0813 (MH^+), calcd for $C_9H_{13}O_4$, 185.0813, m/e 184.0731 (M^+), calcd for $C_9H_{12}O_4$, 184.0736.

Alternative Preparation of Epoxy Lactones 6a and 17a from Allylic Alcohol 32. Allylic alcohol **7a** (82 mg, 0.54 mmol) was added to a 2-mL solution of acetic acid and water [7:1 (v/v)]. The reaction mixture was cooled to 0 °C, followed by the addition of 30% hydrogen peroxide (120 μL, 1.39 mmol, 2.5 equiv). After 20 h at 4 °C, the reaction mixture was poured into ether, washed with brine, and dried. Solvent evaporation in vacuo and purification via PLC (1000 μm, ether) afforded 68 mg (75%) of lactone **32**: IR ($CHCl_3$) 3672 (w, sh), 3200–3650 (s, br), 2875–3075 (s), 1760 (s), 1680 (w), 1425 (m), 1400 (m), 1345 (m), 1175 (s), 1045 (m), 985 (m), 960 (m), 900 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.85 (s, 3 H), 2.05–3.10 (complex, m, 6 H), 4.15–4.40 (m, 1 H), 4.75–5.05 (m, 1 H), 5.60–5.80 (m, 1 H); chemical ionization mass spectrum, m/e 169.0870 (MH^+), calcd for $C_9H_{13}O_3$, 169.0865.

Epoxidation was then effected via two different methods: (A) A catalytic amount of vanadyl acetyl-acetonate [$VO(ACAC)_2$] was added to a solution of the above lactone (63 mg, 0.38 mmol) in 3 mL of benzene. A solution of 72% *tert*-butyl hydrogen peroxide (75 mg, 0.60 mmol) in benzene was added dropwise. The reaction was stirred at room temperature for 3 h and then heated at reflux for 12 h. After cooling to room temperature, the reaction mixture was poured into ether, washed with aqueous sodium bisulfite and brine, and dried over potassium carbonate. Removal of solvent in vacuo afforded 43 mg (61%) of product, which was purified via PLC (500 μm, 3:2 ethyl acetate–ether). The separation yielded 22 mg (32%) of epoxide **6a** and 6.5 mg (9.5%) of epoxide **17a** (3.3:1 ratio), which were identical with **6a** and **17a** previously prepared.

(B) To a solution of **32** (28 mg, 0.17 mmol) in 2 mL of methylene chloride at 0 °C was added 1.25 equiv of *m*-chloroperoxybenzoic acid (43 mg, 0.21 mmol). The reaction mixture was stirred for 2 h and then diluted with methylene chloride, washed with brine, and dried over anhydrous potassium carbonate. Removal of solvent in vacuo afforded 25 mg (84%) of product. Separation by preparative thin-layer chromatography (500 μL, 3:2 ethyl acetate–ether) afforded 17 mg (56%) of **6a** and 5.3 mg (18%) of **17a**; the latter were identical with **6a** and **17a** prepared previously.

Model Study: Preparation of (3aα,7aα)-Hexahydro-3-(4-methyl-3-pentenyl)-2(3*H*)-benzofuranone (20). To a solution of diisopropylamine (145 μL, 1.03 mmol) in 1 mL of tetrahydrofuran cooled to 0 °C under argon was added 397 μL of *n*-butyllithium (0.83 mmol, 2.09 M in hexane). After 15 min, the solution was cooled at −78 °C, and after stirring for an additional 15 min, lactone **18** (97 mg, 0.69 mmol) in 0.5 mL of tetrahydrofuran was added dropwise over a period of 30 min. The mixture was stirred at −78 °C for 1 h, and then 2-methyl-5-iodo-2-pentene (218 mg, 1.04 mmol) was rapidly added dropwise. The reaction mixture was stirred for an additional hour at −78 °C, then warmed slowly to 0–5 °C, and allowed to stand overnight at 4 °C. The reaction was quenched with brine, extracted into ether, washed with brine, dried, and concentrated in vacuo. Purification by flash chromatography [silica gel, 4:1 hexane–ether (v/v)] afforded 129 mg (84%) of lactone **20** as a colorless oil: IR (CCl_4) 2750–3000 (s), 1755 (s), 1445 (m), 1360 (w), 1170 (s), 1130 (m), 960 (s), 905 (m) cm^{-1}; ^1H NMR (250 MHz, $CHCl_3$) δ 0.96–1.94 (complex m, 15 H), 2.0–3.98 (m, 4 H), 2.58–2.70 (m, 1 H), 4.38 (br s, 1 H), 5.04–5.18 (m, 1 H); electron impact mass spectrum, m/e 222.1612 (M^+), calcd for $C_{14}H_{22}O_2$, 222.1620.

5,6,7,7a-Tetrahydro-3-(4-methyl-3-pentenyl)-2(4*H*)-benzofuranone (21). To a solution of diisopropylamine (43 μL, 0.31 mmol) in 1 mL of dry tetrahydrofuran cooled to 0 °C under argon was added 114 μL of *n*-butyllithium (0.26 mmol, 2.3 M). After 15 min, the reaction was cooled to −78 °C, stirred for 15 min, and lactone **20** (49 mg, 0.22 mmol) in 0.5 mL tetrahydrofuran added dropwise over a period of 20 min. The mixture was stirred for 1.5 h at −78 °C, and then a solution of diphenyl diselenide (82 mg, 0.26 mmol) in 0.5 mL of tetrahydrofuran containing hexamethylphosphoramide (46 μL, 0.26 mmol) was rapidly added via syringe. After an additional 1 h at −78 °C, the reaction was slowly warmed to room temperature, quenched with brine, poured into ether, washed with brine, and dried. Removal of solvent in vacuo followed by preparative thin-layer chromatography [1000 μm, 40:60 ether–hexane (v/v)] afforded 41 mg (50%) of the selenide of **20** and 13.5 mg (28%) of lactone **20** (70% based on recovered starting material). The selenide possessed the following spectral data: IR ($CHCl_3$) 2800–3050 (s), 1750 (s), 1445 (m), 1350 (m), 1170 (s), 1130 (m), 1100 (m), 960 (s), 680 (w) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.76–2.78 (complex m, 19 H), 4.82–5.35 (m, 2 H), 7.30–7.66 (m, 5 H).

Oxidative elimination was effected by adding 18 mg of 30% hydrogen peroxide in 15 μL of water to a solution of the selenide (20 mg, 0.05 mmol) in 0.5 mL of tetrahydrofuran at 0 °C. After 10 min, 2 equiv of diisopropylethylamine (18 μL, 0.10 mmol) were added, and the reaction mixture was allowed to come to room temperature. After stirring for an additional 1.5 h, the reaction was poured into ether, washed with water, 5% sodium bicarbonate, and brine, and dried. Removal of the solvent in vacuo followed by preparative thin-layer chromatography [250 μm, 40:60 ether–hexane (v/v)] afforded 7 mg (60%) of unsaturated lactone **21**: IR ($CHCl_3$) 2750–3020 (s), 1745 (s), 1675 (m), 1450 (m), 1375 (w), 1350 (w), 1250 (w), 1110 (m), 1040 (m), 905 (s), 640 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.78–1.76, 1.54, 1.65 (m, s, s, 2 H, 3 H, 3 H), 1.80–2.37 (m, 8 H), 2.44–2.57 (m, 1 H), 2.80 (dd, J = 2.5, 12.5 Hz, 1 H), 4.55 (dd, J = 5.0, 10.0 Hz, 1 H), 4.96–5.12 (m, 1 H); electron impact mass spectrum, m/e 220.1466 (M^+), calcd for $C_{14}H_{20}O_2$, 220.1464.

Preparation of Triethylsilyl Ether 6c. To a solution of triethylsilyl chloride (234 mg, 1.3 equiv), triethylamine (250 μL, 1.79 mmol, 1.5 equiv), and a catalytic amount of dimethylaminopyridine (10.2 mg, 0.07 equiv) in 3 mL of methylene chloride was added alcohol **6a** (220 mg, 1.20 mmol). The reaction was stirred for 12 h under argon at room temperature. The solution was then diluted with methylene chloride, washed with dilute aqueous ammonium chloride, water, and brine, and dried, and the solvent concentrated in vacuo. Flash chromatography on silica gel [40:60 ether–hexane (v/v)] yielded an analytically pure sample of silyl ether **6c** (355 mg, 99.5%): IR (CCl_4) 2850–3050 (s), 1755 (s), 1455 (w), 1420 (m), 1375 (m), 1340 (m), 1200 (m), 1105 (s), 1075 (s), 900 (s), 865 (m), 810 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.60 (q, J = 7.5 Hz, 6 H), 0.92 (t, J = 7.5 Hz, 9 H), 1.30 (s, 3 H), 1.94 (dd, J = 15.0, 5.0 Hz, 1 H), 2.08 (d, J = 15.0 Hz, 1 H), 2.27 (dd, J = 10.0, 20.0 Hz, 1 H), 2.82–2.97 (apparent heptet, J = 10.0, 5.0, 6.0, 6.0 Hz, 1 H), 2.99 (s, 1 H), 3.06 (dd, J = 5.0, 20.0 Hz, 1 H), 4.17 (d, J = 6.0 Hz, 1 H), 4.65 (dd, J = 5.0, 10.0 Hz, 1 H); chemical ionization mass spectrum, m/e 299.1704 (MH^+), calcd for $C_{15}H_{27}O_4Si$, 299.1679.

Preparation of Lactone 22a. To a solution of diisopropylamine (104 μL, 0.74 mmol) in 1 mL of dry tetrahydrofuran under argon cooled to 0 °C was added 304 μL of *n*-butyllithium (0.64 mmol, 2.09 M in hexane). The mixture was stirred for 15 min at 0 °C and then cooled to −78 °C. After an additional 20 min, lactone **6c** (160 mg, 0.54 mmol) in 0.5

mL of tetrahydrofuran was added dropwise over a period of 30 min. The mixture was stirred for 1 h at −78 °C, and a solution of 2-methyl-5-iodo-2-pentene (167 mg, 1.0 mmol) in 0.5 mL of tetrahydrofuran was added rapidly. After an additional hour at −78 °C, the reaction was warmed slowly to 0 °C and allowed to stand at 4 °C for 12 h. The reaction was quenched with brine and poured into ether. The organic layer was washed with brine, dried, and concentrated in vacuo. Purification via flash chromatography on silica gel [4:1 ether–hexane (v/v)] afforded lactone **22a** (144 mg, 71%) as a white crystalline solid (mp 60–61 °C): IR (CCl_4) 2860–2950 (s), 1760 (s), 1440 (w, br), 1360 (m), 1190 (m), 1120 (m, br), 1080 (m), 1020 (m, br), 860 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.69 (q, J = 7.6 Hz, 6 H), 1.02 (t, J = 7.6 Hz, 9 H), 1.36 (s, 3 H), 1.63, 1.58–1.82, 1.70 (s, m, s, 3 H, 2 H, 3 H), 1.96 (dd, J = 4.9, 15.7 Hz, 1 H), 2.04–2.21 (m, 2 H), 2.31 (d, J = 15.7 Hz, 1 H), 2.61 (ddd, J = 10.1, 5.7, 6.3 Hz, 1 H), 2.99 (br s, 1 H), 3.14 (dd, J = 5.7, 6.3 Hz, 1 H), 4.25 (d, J = 6.5 Hz, 1 H), 4.60 (dd, J = 4.9, 5.21 Hz, 1 H), 5.08 (t, J = 7.2 Hz, 1 H); electron impact mass spectrum, m/e 380.2393 (M^+), calcd for $C_{21}H_{36}O_4Si$, 380.2382.

Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 66.27; H, 9.57.

Selenenylation of Lactone 22a. To a solution of a tetramethylpiperidine (60 μL, 0.36 mmol, 1.6 equiv) in 1 mL of dry tetrahydrofuran, under an argon atmosphere, cooled to −20 °C was added 184 μL of *n*-butyllithium (0.29 mmol, 1.6 M in hexane, 1.3 equiv). The mixture was stirred for 15 min, followed by addition of lactone **22a** (85 mg, 0.22 mmol) in 500 μL of tetrahydrofuran over a 20-min period. The reaction mixture was stirred for 1.5 h with slow warming to 0 °C. After which, the solution was recooled to −20 °C and phenylselenenyl chloride (90 mg, 0.47 mmol, 2.1 equiv) in a 1-mL solution of tetrahydrofuran containing 125 μL of hexamethylphosphoramide was added. After warming to 0 °C and an additional 2 h, the reaction was quenched with brine and diluted with ether. The organic layer was washed with brine, dried, and concentrated in vacuo. Flash chromatography on silica gel [4:1 hexane–ether (v/v)] afforded 26 mg of starting material (**22a**) and 40 mg of the desired selenide **23a**; the yield was 49% on the basis of recovered lactone. Selenide **23a** was isolated as a white crystalline solid (mp 128–130 °C): IR ($CHCl_3$) 2850–3050 (s), 1760 (s), 1670 (w), 1440 (m), 1390 (m), 1300 (w), 1200 (s), 1120 (m), 1020 (m), 920 (m), 840 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.65 (q, J = 9.8 Hz, 6 H), 0.99 (t, J = 9.8 Hz, 9 H), 1.40 (s, 3 H), 1.69 (s, 3 H), 1.73 (s, 3 H), 1.91–2.11 (m, 3 H), 2.13–2.33 (m, 2 H), 2.46 (dd, J = 3.5, 7.7 Hz, 1 H), 2.61–2.82 (m, 1 H), 2.98 (d, J = 3.07 Hz, 1 H), 4.20 (t, J = 3.30 Hz, 1 H), 4.28 (dd, J = 7.7, 13.2 Hz, 1 H), 4.90 (t, J = 7.7 Hz, 1 H), 7.25–7.44 (m, 3 H), 7.58–7.64 (m, 2 H); chemical ionization mass spectrum, m/e 537.1953 (MH^+), calcd for $C_{27}H_{41}O_4SiSe$, 537.1939.

Preparation of (±)-Paniculide A (1) Directly from 23a. To a saturated solution of sodium periodate in 0.5 mL of water under argon was added selenide **23a** (20 mg, 0.038 mmol) in 0.5 mL of tetrahydrofuran. After 45 min, the reaction mixture was poured into ether, washed with brine, dried, and evaporated in vacuo. Purification on silica gel (250 μm, ether) afforded 7.2 mg (0.027 mmol, 73%) of (±)-paniculide A (**1**) as a white crystalline solid (mp 99–100 °C). Racemic paniculide A, identical in all respects (IR, 250-MHz, NMR, MS, TLC mobility) with a sample of the natural product generously supplied by Professor Overton,[30] had the following spectral characteristics: IR ($CHCl_3$) 3350–3600 (m, br), 3010 (m), 2850–3000 (m), 1750 (s), 1670 (w), 1440 (m), 1375 (m), 1340 (m), 1210 (s), 1105 (m), 1050 (m), 1000 (w), 850 (w), 720 (s, br), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.46 (s, 3 H), 1.58 (s, 3 H), 1.77 (s, 3 H), 1.85 (dd, J = 9.0, 14.3 Hz, 1 H), 2.0–2.33 (m, 2 H), 2.44–2.69 (m, 4 H), 3.25 (d, J = 2.7 Hz, 1 H), 4.69 (t, J = 9.0 Hz, 1 H), 4.92 (d, J = 11.7 Hz, 1 H), 5.18 (t, J = 7.6 Hz, 1 H); electron impact mass spectrum, m/e 264.1362 (M^+), calcd for $C_{15}H_{20}O_4$, 264.1362.

Preparation of Lactone 24a. To a solution of selenide **23a** (25.2 mg, 0.047 mmol) in 2 mL of methylene chloride containing 4 equiv of pyridine (17 μL, 0.20 mmol) was added 0.25 mmol of hydrogen peroxide (28 mg of 30% H_2O_2 in 23 μL of water); after 1.5 h at 25 °C, the reaction mixture was poured into ether, washed with brine, dried, and concentrated to dryness in vacuo. Flash chromatography on silica gel [7:3 hexane–ether (v/v)] afforded 15 mg (85%) of a colorless oil: IR ($CHCl_3$) 2750–3040 (s), 1755 (s), 1685 (w), 1455 (w), 1390 (m), 1330 (m), 1210–1250 (m, br), 1120 (s), 1010 (m), 995 (w), 910 (m), 840 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80 (q, J = 8.0 Hz, 6 H), 1.09 (t, J = 8.0 Hz, 9 H), 1.47 (s, 3 H), 1.64 (s, 3 H), 1.72 (s, 3 H), 1.92 (dd, J = 8.8, 14.1 Hz, 1 H), 2.16–2.28 (m, 2 H), 2.49–2.64 (m, 3 H), 3.13 (s, 1 H), 4.68 (t, J = 8.8 Hz, 1 H), 5.05–5.21 (m, 2 H); chemical ionization mass spectrum, m/e 379.2302 (MH^+), calcd for $C_{21}H_{35}O_4Si$, 379.2305, m/e 378.2225 (M^+), calcd for $C_{21}H_{34}O_4Si$, 378.2227.

Preparation of (±)-Paniculide A (1) via Silyl Ether 24a. Silyl ether **24a** (15 mg, 0.04 mmol) was dissolved in a 1-mL solution of acetic acid–tetrahydrofuran–water [3:2:2 (v/v/v)] and stirred overnight at room temperature under argon. The reaction mixture was evaporated to dryness in vacuo to give 10 mg (0.04 mmol, 95%) of (±)-paniculide A. Purification on silica gel afforded a white crystalline solid (mp 99–100 °C), which was identical in all respects with (±)-paniculide A previously prepared.

4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-7,7-diethoxybicyclo[4.2.0]octan-2-one (9b). A degassed solution containing enone **13a** (12.19 g, 0.051 mol) and 1,1-diethoxyethylene (25.2 g, 0.217 mol) in dry benzene was irradiated with a Hanovia 450-W mercury arc lamp fitted with a Pyrex filter for 3.5 h. The reaction was monitored by thin-layer chromatography [75% ether–hexane (v/v)]. The solvent was removed in vacuo and the excess 1,1-diethoxyethylene removed via distillation through a short Vigreux column. Flash chromatography [silica gel, 25:75 ether–hexane (v/v)] afforded **25** as a mixture of diastereomers (16.19 g, 90%), which were not separated: IR ($CHCl_3$) 2850–3030 (s), 1690 (s), 1455 (m), 1380 (m), 1305 (m), 1250 (s), 1160 (m), 1120 (s), 1050 (s), 820 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.95 (s, 9 H), 1.04–1.14 (m, 6 H), 1.46–2.76 (complex m, 9 H), 3.22–3.62 (m, 6 H); electron impact mass spectrum, m/e 356.2397 (M^+), calcd for $C_{19}H_{36}O_4Si$, 356.2384.

4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-7,7-diethoxybicyclo[4.2.0]oct-3-en-2-one (8b). A solution of tetramethylpiperidine (1.89 mL, 11.2 mmol) in dry tetrahydrofuran under argon was cooled to 0 °C, and 4.25 mL of *n*-butyllithium (9.72 mmol, 2.3 M) in hexane was added. After 15 min, ketone **9b** (2.66 g, 7.48 mmol) in 0.5 mL of tetrahydrofuran was added dropwise. The reaction was slowly warmed to room temperature. After an additional 45 min, triethylamine (5.21 mL, 37.4 mmol, 5 equiv), and trimethylsilyl chloride (4.75 mL, 37.4 mmol, 5 equiv) were mixed quickly in 10 mL of tetrahydrofuran and added to the reaction mixture. The resultant mixture was allowed to stand at room temperature for 3 h, after which the solution was poured into cold 10% aqueous sodium bicarbonate, extracted with ether, dried, and evaporated in vacuo to afford 3.11 g (97%) of enol silyl ether **25**, which was carried on to the next step without purification; IR (CCl_4) 2850–3000 (s), 1620 (w), 1450 (m), 1375 (m), 1250 (s), 1265 (s), 1075 (s, br), 850 (s, br) cm^{-1}.

A mixture of 838 mg of palladium acetate (3.74 mmol, 0.5 equiv) and 404 mg of *p*-benzoquinone (3.74 mmol, 0.5 equiv) was dissolved in 80 mL of dry acetonitrile. To this homogeneous solution was added **25** (2.87 g, 6.68 mmol) in 20 mL of acetonitrile. After 21 h, the palladium salts were removed, and the filtrate was diluted with ether, washed with sodium bicarbonate and water, and dried. After filtration through a silica pad, concentration in vacuo afforded a mixture of **8b** and **26** as well as recovered starting material. The three components were separated via flash chromatography on silica gel [15:85 ether–hexane (v/v)]. Ketone **9b** eluted first (288 mg, 11%), followed by **26** and **8b**, the latter isolated as colorless oils.

26 (major product, 699 mg, 26%): IR ($CHCl_3$) 2850–3025 (s), 1675 (s), 1605 (w), 1450 (m), 1360 (m), 1240 (m, br), 1140 (m), 1070 (m), 1050 (s), 1035 (m), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.97 (s, 9 H), 1.25 (q, J = 6.57 Hz, 6 H), 2.16–2.70 (complex m, 6 H), 3.34–3.60 (complex m, 4 H), 4.09 (AB quartet, J_{AB} = 16.3 Hz, 2 H), 5.95 (s, 1 H); chemical ionization mass spectrum, m/e 355.2303 (MH^+), calcd for $C_{19}H_{35}O_4Si$, 355.2305.

Cis isomer 8b (344 mg, 13%): IR ($CHCl_3$) 2850–3050 (s), 1650 (s), 1425 (m), 1375 (m), 1250 (s), 1150 (m), 1045 (m), 920 (m), 830 (s), 780 (s, br), 720 (s, br), 660 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 0.98 (s, 9 H), 1.14 (t, J = 7.30 Hz, 3 H), 1.24 (t, J = 6.8 Hz, 3 H), 2.02–2.48 (complex m, 4 H), 2.83 (apparent sextet, J = 4.2, 9.4, 8.3 Hz, 1 H), 3.11 (br t, J = 9.4 Hz, 1 H), 3.30–3.54 (m, 4 H), 4.22 (AB quartet, J_{AB} = 17.7 Hz, 2 H), 6.15 (s, 1 H); chemical ionization mass spectrum, m/e 355.2302 (MH^+), calcd for $C_{19}H_{35}O_4Si$, 355.2304, m/e 354.2231 (M^+), calcd for $C_{19}H_{34}O_4Si$, 354.2227.

Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.69; H, 9.72.

Preparation of Enone 8b via Equilibration. The conversion of the mixture of cis and trans isomers **8b** and **26**, respectively, to **8b** under mild conditions is best illustrated by the following two experiments.

(A) Treatment with Hydroxide. A sample containing both isomers (167 mg, 0.47 mmol) was stirred for 3 h with 0.3 mL of 2% potassium hydroxide in 3 mL of methanol and 0.3 mL of water. The reaction mixture was then poured into ether, washed with brine, dried, and concentrated in vacuo. Silica gel flash chromatography (3:1 hexane–ether) afforded 142 mg (85%) of **8b** as a colorless oil having spectral properties identical with those previously described.

(B) Filtration through Alumina.[37] A sample containing both isomers (0.2416 g, 0.68 mmol) was placed on a neutral alumina column for 30 min, eluted with ether followed by removal of the solvent in vacuo affording 219 mg (91%) of a single isomer **8b** having spectral properties

identical with those previously described.

(1α,2β,6α)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-7,7-diethoxybicyclo[4.2.0]oct-3-en-2-ol (16b). Enone **8b** (535 mg, 1.51 mmol) was dissolved in 3.8 mL of methanolic cerium(III) chloride (0.4 M). The reaction mixture was cooled to 0 °C and sodium borohydride (57 mg, 1.51 mmol) added slowly. The mixture was allowed to stir for 10 min, followed by addition of water to destroy excess sodium borohydride. The solution was poured into ether, washed with brine, and dried. Removal of solvent in vacuo afforded 489 mg (91%) of **16b** as a pale yellow oil. An analytical sample was obtained via flash chromatography [4:1 hexane–ether (v/v)]: IR ($CHCl_3$) 3610 (m, sh), 3250–3500 (w, br), 2875–3025 (s), 1455 (m), 1380 (m), 1300 (w), 1250 (m, br), 1150 (m), 1090 (m), 1040 (s), 990 (w), 920 (w), 890 (w), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 3 H), 0.15 (s, 3 H), 1.0 (s, 9 H), 1.16 (t, J = 7.05 Hz, 3 H), 1.29 (t, J = 7.35 Hz, 3 H), 1.70 (br s, 1 H), 1.79–1.96 (m, 2 H), 2.04–2.16 (m, 2 H), 2.60–2.83 (m, 2 H), 3.24–3.47 (complex m, 4 H), 4.11 (AB quartet, J_{AB} = 17.5 Hz, 2 H), 4.32 (br s, 1 H), 5.67 (s, 1 H); chemical ionization mass spectrum, m/e 357.2392 (MH^+), calcd for $C_{29}H_{37}O_4Si$, 357.2379, m/e 356.2340 (M^+), calcd for $C_{19}H_{36}O_4Si$, 356.2384.

(1α,2β,6α)-4-[[[(Dimethylethyl)dimethylsilyl]oxy]methyl]-2-hydroxybicyclo[4.2.0]oct-3-en-7-one (7b). Bicyclic ketal **16b** (654 mg, 1.84 mmol) and 0.3 equiv of pyridinium *p*-toluenesulfonate (115 mg, 0.459 mmol) were taken up in 15 mL of 2-butanone (dried over potassium carbonate) and maintained at reflux for 10 min under argon. After cooling, the reaction mixture was poured into ether, washed with sodium bicarbonate and brine, dried over anhydrous potassium carbonate, and concentrated in vacuo to give 473 mg (91%) of a white crystalline solid. An analytical sample of **7b** was prepared by silica gel flash chromatography [1:1 ether–hexane]: mp 59–60 °C; IR ($CHCl_3$) 3605 (m, sh), 3300–3550 (m, br), 2850–3050 (s), 1770 (s), 1690 (m), 1650 (w), 1455 (m), 1375 (m), 1250 (s, br), 1100 (s, br), 940 (w), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 6 H), 0.97 (s, 9 H), 1.82 (d, J = 3.4 Hz, 1 H), 2.01 (dd, J = 16.3, 7.7 Hz, 1 H), 2.23 (dd, J = 16.3 Hz, 1.25 Hz, 1 H), 2.78–2.94 (complex m, 1 H), 2.98–3.12 (complex m, 2 H), 3.42–3.58 (m, 1 H), 4.04 (AB quartet, J_{AB} = 18.5 Hz, 2 H), 4.63 (br s, 1 H), 5.77 (s, 1 H); chemical ionization mass spectrum, m/e 283.1711 (MH^+), calcd for $C_{15}H_{27}O_3Si$, 283.1729.

Anal. Calcd for $C_{15}H_{26}O_3Si$: C, 63.79; H, 9.28. Found: C, 63.78; H, 9.31.

Preparation of Epoxy Lactones 6b and 17b. To a solution of allylic alcohol **7b** (58 mg, 0.204 mmol) in 3 mL of dry methylene chloride containing suspended sodium bicarbonate (56 mg, 0.67 mmol) at 0 °C was added 3 equiv of *m*-chloroperoxybenzoic acid (127 mg, 0.613 mmol). This solution was allowed to stand at 5 °C for 18 h. Anhydrous potassium carbonate was added, and the mixture was stirred for 1 h. Removal of the precipitated salts and solvents in vacuo followed by purification via silica gel flash chromatography employing ether as eluent afforded epoxy lactones **6b** and **17b** in a ratio of 3:1.

The major isomer, **6b** (47 mg, 0.15 mmol, 74%), was a white crystalline solid: mp 87–88 °C; IR ($CHCl_3$) 3600 (w, sh), 3250–3550 (w, br), 2850–3050 (m), 1755 (s), 1450 (m), 1400 (w), 1360 (m), 1250 (m), 1100 (s), 1040 (m), 1000 (m), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.10 (s, 3 H), 0.12 (s, 3 H), 0.94 (s, 9 H), 2.07 (dd, J = 5.5, 16.55 Hz, 1 H), 2.27–2.62 (complex m, 3 H), 2.96–3.15 (m, 2 H), 3.32 (s, 1 H), 3.68 (AB quartet, J_{AB} = 11.7 Hz, 2 H), 4.31 (s, br, 1 H), 4.78 (dd, J = 5.5, 9.0 Hz, 1 H); chemical ionization mass spectrum, m/e 315.1617 (MH^+), calcd for $C_{17}H_{27}O_5Si$, 315.1627.

The minor isomer, **17b** (16 mg, 0.05 mmol, 25%), was a white crystalline solid: mp 117–118 °C; IR ($CHCl_3$) 3610 (w, sh), 3300–3550 (w, br), 2860–3050 (s), 1765 (s), 1460 (m), 1410 (w), 1375 (m), 1320 (w), 1250 (s, br), 1155 (m), 1100 (s, br), 995 (m), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 1.0 (s, 9 H), 2.36 (dd, J = 5.5, 15.8 Hz, 1 H), 2.60–2.84 (m, 5 H), 3.38 (d, J = 4.1 Hz, 1 H), 3.76 (AB quartet, J_{AB} = 11.6 Hz, 2 H), 4.38 (s br, 1 H), 4.70–4.82 (m, 1 H); chemical ionization mass spectrum, m/e 315.1638 (MH^+), calcd for $C_{15}H_{27}O_5Si$, 315.1627.

Preparation of Triethylsilyl Ether 6d. A mixture of triethylsilyl chloride (255 mg, 1.70 mmol), triethylamine (273 μL, 1.96 mmol), and a catalytic amount of dimethylaminopyridine (11.2 mg, 0.07 equiv) in 5 mL of methylene chloride was allowed to stir for 10 min followed by addition of alcohol **6b** (410 mg, 1.31 mmol). The reaction mixture was stirred for 1.5 h under argon at room temperature. Workup consisted of addition to methylene chloride, washing with dilute ammonium chloride, water and brine, drying, and solvent removal by evaporation. Flash chromatography [silica gel, 4:1 hexane–ether (v/v)] afforded 452 mg (81%) of silyl ether **6d**: IR ($CHCl_3$) 2850–3050 (s), 1755 (s), 1450 (m), 1400 (w), 1355 (m), 1330 (w), 1250 (m, br), 1110 (s), 1050 (m), 1005 (m), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.9 (s, 3 H), 0.11 (s, 3 H), 0.65 (q, J = 10.0 Hz, 6 H), 0.95 (s, 9 H), 1.02 (t, J = 10.0 Hz, 9 H), 2.02 (dd, J = 5.7, 16.2 Hz, 1 H), 2.38 (d, J = 16.2 Hz, 1 H), 2.43 (dd, J = 11.2, 18.4 Hz, 1 H), 2.96 (apparent heptet, J = 7.0, 7.0, 5.6, 11.2 Hz, 1 H), 3.11 (dd, J = 5.9, 18.4 Hz, 1 H), 3.19 (s, 1 H), 3.68 (AB quartet, J_{AB} = 11.8, 2 H), 4.21 (d, J = 7.0 Hz, 1 H), 4.75 (apparent octet, J = 1.5, 5.3, 5.3, 5.7 Hz, 1 H); chemical ionization mass spectrum, m/e 429.2510 (MH^+), calcd for $C_{21}H_{41}O_5Si_2$, 429.2492.

Preparation of Lactone 22b. To a solution of diisopropylamine (90 μL, 0.635 mmol) in 1 mL of dry tetrahydrofuran at 0 °C under argon was added 345 μL of *n*-butyllithium (0.58 mmol, 1.67 M in hexane). After cooling to −78 °C for 15 min, lactone **6d** (182 mg, 0.43 mmol) in 1 mL of tetrahydrofuran was added dropwise over a period of 20 min. The reaction was stirred for 1 h at −78 °C, whereupon a solution of 2-methyl-5-iodo-2-pentene (152 mg, 0.72 mmol) in 0.5 mL of tetrahydrofuran was added rapidly in a dropwise fashion. After an additional 1 h at −78 °C, the reaction mixture was warmed slowly to 0 °C and allowed to stand overnight at 4 °C. The reaction was quenched with brine, diluted with ether, washed with water and brine, and dried over anhydrous potassium carbonate. Evaporation of the solvent in vacuo followed by flash chromatography on silica gel [4:1 ether–hexane (v/v)] afforded 157 mg (72%) of **22b** as a white crystalline solid: mp 45–46 °C; IR ($CHCl_3$) 2850–3050 (s), 1765 (s), 1455 (m), 1355 (m), 1330 (w), 1240 (m, br), 1100 (s), 1040 (m), 1000 (m), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.71 (q, J = 8.7 Hz, 6 H), 0.98 (s, 9 H), 1.07 (t, J = 8.7 Hz, 9 H), 1.61–1.79, 1.64, 1.73 (m, s, s, 2 H, 3 H, 3 H), 2.03 (dd, J = 5.1, 16.0 Hz, 1 H), 2.09–2.24 (m, 2 H), 2.38 (d, J = 16.0 Hz, 1 H), 2.58–2.72 (m, 1 H), 3.13–3.23, 3.19 (m, s, 1 H, 1 H), 3.66 (AB quartet, J_{AB} = 11.5 Hz, 2 H), 4.29 (d, J = 6.7 Hz, 1 H), 4.70 (dd, J = 5.1, 10.6 Hz, 1 H), 5.13 (t, J = 7.5 Hz, 1 H); chemical ionization mass spectrum, m/e 511.3237 (MH^+), calcd for $C_{27}H_{51}O_5Si$, 511.3275, m/e 510.3156 (M^+), calcd for $C_{27}H_{50}O_5Si$, 510.3197.

Anal. Calcd for $C_{27}H_{50}O_5Si$: C, 63.48; H, 9.87. Found: C, 63.24; H, 9.99.

Attempted Selenenylation of Lactone 22b without Oxidation of Phenylselenenyl Anion. To a solution of 430 μL of potassium bis(trimethylsilyl)amide (0.29 mmol, 0.67 M) in 1 mL of dry tetrahydrofuran cooled to −100 °C under argon was added a solution of lactone **22b** (42 mg, 0.083 mmol) in 0.5 mL of tetrahydrofuran. The reaction mixture was stirred at −100 °C for an additional 10 min, whereupon diphenyl diselenide (129 mg, 0.41 mmol) in 0.5 mL of tetrahydrofuran containing 75 μL of hexamethylphosphoramide (0.41 mmol) was added. The resulting mixture was then warmed to −10 °C over a period of 3 h, quenched with brine, and added to ether. The ethereal solution was extracted with brine, dried, and concentrated in vacuo. Flash chromatography on silica gel [85:15 hexane–ether] afforded 11.5 mg of the α isomer **29** and 14.9 mg of the β isomer **22b**. Spectral properties of the β isomer **22b** are recorded above.

α Isomer 29a: mp 65–66 °C; IR ($CHCl_3$) 2800–3050 (s), 1760 (s), 1455 (m), 1355 (m), 1250 (s), 1100 (s), 1000 (m), 905 (s), 825 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.14 (s, 3 H), 0.71 (q, J = 9.1 Hz, 6 H), 0.98 (s, 9 H), 1.06 (t, J = 9.1 Hz, 9 H), 1.70 (s, 3 H), 1.76 (s, 3 H), 1.82–2.12 (complex m, 3 H), 2.18–2.32 (m, 2 H), 2.42–2.70 (m, 3 H), 3.11 (d, J = 11.40 Hz, 1 H), 3.48 (d, J = 11.4 Hz, 1 H), 3.80 (s, J = 11.4 Hz, 1 H), 4.39 (t, J = 3.4 Hz, 1 H), 4.61 (dd, J = 6.8, 13.7 Hz, 1 H), 5.13 (t, J = 8.0 Hz, 1 H); chemical ionization mass spectrum, m/e 511.3279 (MH^+), calcd for $C_{27}H_{51}O_5Si$, 511.3275, m/e 510.3189 (M^+), calcd for $C_{27}H_{50}O_5Si$, 510.3197.

Selenenylation of Lactone 22b with Oxidation of Phenylselenenyl Anion. To a solution consisting of 580 μL of potassium bis(trimethylsilyl)amide (0.39 mmol, 0.68 M) in 1 mL of dry tetrahydrofuran cooled to −100 °C under argon was added a solution of lactone **22b** (65 mg, 0.13 mmol) in 0.5 mL of tetrahydrofuran. After the mixture was stirred for 10 min at −100 °C, diphenyl diselenide (205 mg, 0.66 mmol) in 0.5 mL of a 5:1 tetrahydrofuran–hexamethylphosphoramide solution was added. The resulting mixture was then allowed to stir for 1.5 h at −100 °C, followed by slow warming to −20 °C over a period of 1 h. After the solution was stirred for 45 min at −20 °C, the reaction was cooled to −78 °C and oxygen was bubbled into the solution for 1 h. The reaction was quenched with brine, poured into ether, the organic layer washed with water and brine, dried, and the solvent removed in vacuo. Flash chromatography on silica gel [15:85 ether–hexane] afforded 33 mg of starting material **22b** and 34 mg of the desired selenide **23b** (82% based on recovered starting material). The selenide **23b** was a white crystalline solid: mp 97–98 °C; IR (CCl_4) 2800–3025 (s), 1755 (s), 1455 (m), 1360 (w), 1310 (w), 1260 (m), 1185 (s), 910 (w), 835 (s), 720 (m), 685 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 3 H), 0.16 (s, 3 H), 0.66 (q, J = 7.1 Hz, 6 H), 0.96–1.03, 1.0 (t, J = 7.1 Hz, s, 9 H, 9 H), 1.73 (s, 3 H), 1.76 (s, 3 H), 1.84–2.08, 1.91 (m, dd, J = 6.8, 14.3 Hz, 2 H, 1 H), 2.12–2.34, 2.29 (m, dd, J = 2.8, 6.8 Hz, 1 H, 1 H), 2.59 (dd, J = 8.1, 14.3 Hz, 1 H), 2.64–2.80 (m, 1 H), 3.07 (d, J = 3.7 Hz, 1 H),

3.44 (d, J = 10.7 Hz, 1 H), 3.80 (d, J = 10.7 Hz, 1 H), 4.50 (dd, J = 3.3, 3.3 Hz, 1 H), 4.80 (dd, J = 7.35, 15.25 Hz, 1 H), 5.11 (t, J = 7.0 Hz, 1 H), 7.30–7.42 (m, 3 H), 7.54–7.64 (m, 2 H); chemical ionization mass spectrum, m/e 667.2807 (MH^+), calcd for $C_{33}H_{55}O_5Si_2Se$, 667.2753, m/e 666.2720 (M^+), calcd for $C_{33}H_{54}O_5Si_2Se$, 666.2675.

Preparation of Lactone 24b. To a solution of selenide **23b** (18 mg, 0.03 mmol) in 1 mL of methylene chloride containing 4 equiv of diisopropylethylamine (16 mg, 0.17 mmol) was added 0.17 mmol of hydrogen peroxide (19 mg of 30% H_2O_2 in 16 μL of water); the reaction mixture was then stirred at 25 °C for 3 h. The resultant selenoxide was then heated to reflux for 3 h to effect elimination. After cooling, the reaction mixture was poured into ether, washed with water, sodium bicarbonate, and brine, dried, and concentrated in vacuo. Preparative thin-layer chromatography [250 μm, ether] afforded 13.1 mg (95%) of **24b** as a white waxy solid: mp 53–54 °C; IR ($CHCl_3$) 2780–3090 (s), 1750 (s), 1450 (m), 1380 (s), 1350 (m), 1200–1280 (m, br), 1160 (m), 1120 (s), 1085 (m), 1010 (w), 840 (m), 720 (w), 660 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.76 (q, J = 7.9 Hz, 6 H), 0.97 (s, 9 H), 1.03 (t, J = 7.9 Hz, 9 H), 1.60 (s, 3 H), 1.69 (s, 3 H), 1.76 (dd, J = 4.75, 10.1 Hz, 1 H), 2.10–2.28 (m, 2 H), 2.50–2.59 (m, 2 H), 2.68 (dd, J = 10.1, 14.3 Hz, 1 H), 3.30 (d, J = 1.5 Hz, 1 H), 3.66 (AB quartet, J_{AB} = 11.8 Hz, 2 H), 4.66 (t, J = 8.8 Hz, 1 H), 5.06–5.16 (m, 2 H); chemical ionization mass spectrum, m/e 509.3132 (MH^+), calcd for $C_{27}H_{49}O_5Si_2$, 509.3119, m/e 508.3031 (M^+), calcd for $C_{27}H_{48}O_5Si$, 508.3040.

Preparation of (±)-Paniculide B (2) via Silyl Ether 24b. Bis(silyl ether) **24b** (78.6 mg, 0.15 mmol) was dissolved in 7 mL of acetic acid–tetrahydrofuran–water [3:2:2 (v/v/v)] and stirred overnight at 25 °C under argon. Evaporation in vacuo and preparative thin-layer chromatography (500 μm, ethyl acetate) afforded 38.5 mg of (±)-paniculide B (89%) as a white crystalline solid: mp 126–127 °C; IR ($CHCl_3$) 3340–3650 (m, br), 2825–3050 (m), 1700 (s), 1430 (m), 1375 (m), 1340 (m), 1210 (m), 1150 (w), 1125 (m), 1090 (m), 1065 (m), 1045 (m), 970 (w), 910 (w), 860 (w), 720 (m, br), 660 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.62, 1.60–1.92, 1.80 (s, m, s, 3 H, 2 H, 3 H), 2.12–2.36 (m, 2 H), 2.42–2.72 (m, 4 H), 3.54 (d, J = 2.6 Hz, 1 H), 3.62–3.82 (m, 2 H), 4.70 (t, J = 9.4 Hz, 1 H), 4.98 (d, J = 10.7 Hz, 1 H), 5.17 (t, J = 7.7 Hz, 1 H); chemical ionization mass spectrum, m/e 281.1386 (MH^+), calcd for $C_{15}H_{21}O_5$, 281.1389, m/e 280.1312 (M^+), calcd for $C_{15}H_{20}O_5$, 280.1311.

Synthetic paniculide B was identical in all respects (IR, 250-MHz ^1H and ^{13}C NMR, MS, TLC mobility) with a sample of the natural product generously supplied by Professor Overton.[30]

Selenenylation of Lactone 22a with Oxidation of Phenylselenenyl Anion. To a solution of potassium bis(trimethylsilyl)amide (1.10 mL, 0.77 mmol, 0.70 M) in 1 mL of dry tetrahydrofuran cooled to −100 °C under argon was added lactone **22a** (97 mg, 0.26 mmol) in 0.5 mL of tetrahydrofuran. After the solution was stirred for 10 min at −100 °C, a mixture of diphenyl diselenide (399 mg, 1.28 mmol) in 1 mL of a 5:1 tetrahydrofuran–hexamethylphosphoramide solution (v/v) was added, and the resulting mixture was allowed to stir for 1.5 h at −100 °C. The reaction mixture was then slowly warmed to −20 °C over a period of 1 h. After maintaining the solution at −20 °C for 45 min, the mixture was cooled to −78 °C and oxygen was bubbled into the solution for 1 h. The resulting mixture was quenched with 1 mL of brine, extracted into ether, washed with brine, dried, and evaporated to dryness in vacuo. Flash chromatography [silica gel, 20:80 ether–hexane (v/v)] afforded 38 mg of starting material (**22a**) and 61 mg of selenide **23a** (72% based on recovered starting material). The selenide, a white crystalline solid (mp 128–130 °C) had the same spectral data as previously recorded.

(±)-Paniculide C (3). A mixture of (±)-paniculide B (8.4 mg, 0.03 mmol) and manganese dioxide (13 mg, 0.15 mmol) in 1 mL of methylene chloride was stirred under argon for 2.5 h. The reaction mixture was filtered through a pad of silica gel and the solvent evaporated under reduced pressure. Purification via preparative thin-layer chromatography [250-μm plate, ether] afforded 5.3 mg (64%) of (±)-paniculide C as a pale yellow oil: IR ($CHCl_3$) 3350–3675 (w, br), 2825–3050 (m), 1760 (s), 1705 (m), 1440 (m), 1375 (m), 1350 (m), 1220 (m, br), 1120 (w), 1085 (m), 1040 (m), 990 (w), 820 (w), 750 (w, br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.54 (s, 3 H), 1.64 (s, 3 H), 1.76–1.94 (m, 1 H), 2.05 (dd, J = 4.35, 10.4 Hz, 1 H), 2.26 (q, J = 7.35 Hz, 2 H), 2.42–2.72 (m, 2 H), 2.85 (dd, J = 8.5, 14.35 Hz, 1 H), 3.50 (s, 1 H), 3.86 (AB quartet, J_{AB} = 22.0 Hz, 2 H), 5.03 (t, J = 7.35 Hz, 1 H), 5.16 (t, J = 9.0 Hz, 1 H); chemical ionization mass spectrum, m/e 279.1241 (MH^+), calcd for $C_{15}H_{19}O_5$, 279.1232, m/e 278.1167 (M^+), calcd for $C_{15}H_{18}O_5$, 278.1154.

(±)-Paniculide D (4). Method A. A mixture of (±)-paniculide A (4 mg, 0.02 mmol) and pyridinium chlorochromate (8 mg, 0.04 mmol) in 2 mL of methylene chloride was stirred under argon at room temperature for 2 h. Removal of solvent in vacuo followed by purification via preparative thin-layer chromatography (250 μm, ether) afforded 2.7 mg (68%) of a yellow oil (**4**, (±)-paniculide D): IR ($CHCl_3$) 2850–3050 (m), 1755 (s), 1705 (m), 1440 (m), 1375 (m), 1325 (m), 1220 (m), 1085 (m), 1060 (m), 990 (w), 740 (s), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.52 (s, 3 H), 1.55 (s, 3 H), 1.64 (s, 3 H), 2.14 (dd, J = 10.3, 4.0 Hz, 1 H), 2.24 (q, J = 7.35 Hz, 2 H), 2.42–2.66 (m, 2 H), 2.83 (dd, J = 8.5, 14.35 Hz, 1 H), 3.15 (s, 1 H), 5.03 (t, J = 7.15 Hz, 1 H), 5.14 (t, J = 9.0 Hz, 1 H); electron impact mass spectrum, m/e 262.1205 (M^+), calcd for $C_{15}H_{18}O_4$, 262.1205.

Method B. A mixture of (±)-paniculide A (7.7 mg, 0.029 mmol) and manganese dioxide (12.7 mg, 0.15 mmol) in 1 mL of methylene was stirred under argon for 3 h. The reaction mixture was filtered through a pad of silica gel and then the solvent evaporated under reduced pressure. Purification via preparative thin-layer chromatography (250 μm, ether) afforded 4.7 mg (61%) of (±)-paniculide D as a yellow oil, which was identical via NMR, IR, and TLC mobility with **4** prepared via pyridinium chlorochromate oxidation.

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Registry No. (±)-**1**, 79815-33-1; (±)-**2**, 84048-30-6; (±)-**3**, 84048-31-7; (±)-**4**, 84011-62-1; (±)-**6a**, 79802-65-6; (±)-**6b**, 84011-63-2; (±)-**6c**, 79802-66-7; (±)-**6d**, 84011-64-3; (±)-**7a**, 84011-65-4; (±)-**7b**, 84011-66-5; (±)-**8a**, 79802-63-4; (±)-**8b**, 84027-45-2; **9a**, 84048-32-8; **9b**, 84011-67-6; (±)-**12a**, 79802-61-2; (±)-**12b**, 84011-68-7; (±)-**13a**, 84011-69-8; (±)-**13b**, 84011-70-1; **14**, 118-41-2; (±)-**15a**, 84011-71-2; (±)-**15b**, 64180-76-3; (±)-**16a**, 84027-46-3; (±)-**16b**, 84011-72-3; (±)-**17a**, 84011-73-4; (±)-**17b**, 84011-74-5; (±)-**18**, 74708-15-9; **20**, 84011-75-6; **20** (phenyl selenide), 84011-76-7; (±)-**21**, 84011-77-8; (±)-**22a**, 84011-78-9; (±)-**22b**, 84011-79-0; (±)-**23a**, 84011-80-3; (±)-**23b**, 84011-81-4; (±)-**24a**, 84011-82-5; (±)-**24b**, 84011-83-6; **25**, 84011-84-7; (±)-**26**, 84011-85-8; (±)-**29a**, 84011-86-9; (±)-**30**, 64837-59-8; (±)-**31**, 74785-87-8; (±)-**32**, 84011-87-0; methyl iodide, 74-88-4; 8,8-diethoxy-3-methyl-5-oxobicyclo[4.2.0]octane-3-carboxylic acid, 84011-88-1; *tert*-butyldimethylsilyl chloride, 18162-48-6; 1,1-diethoxyethylene, 2678-54-8; 2-methyl-5-iodo-2-pentene, 43161-11-1; diphenyl diselenide, 1666-13-3; triethylsilyl chloride, 994-30-9; *m*-anisic acid, 586-38-9.