(3.26 g of **26**; 95% recovery) showed a resonance (δ 3.68) only for methanesulfonyl chloride (**26**). Treatment of the aqueous phase with benzylthiuronium chloride gave neither benzylthiuronium methanesulfinate nor benzylthiuronium methanesulfonate (absence of methanesulfinic acid (**24**) and methanesulfonic acid).[48,49]

Attempted Reaction of *S*-Methyl Methanesulfonothioate (12) with Activated Zinc at 0 °C. The experimental procedure described above for zinc and methanesulfonyl chloride (**26**) at 0 °C for 1 h was repeated except thiosulfonate **12** was substituted for **26**.[9a] After the workup, ^{1}H NMR analysis showed the presence of **12** (92% recovery). Treatment of the aqueous phase with benzylthiuronium chloride did not produce a precipitate (absence of methanesulfinic acid (**24**) and methanesulfonic acid).[48,49]

Attempted Reaction of *S*-Methyl Methanesulfonothioate (12) with Anhydrous Zinc Chloride at 0 °C. A 10-mL round-bottomed flask fitted with a serum stopper and containing 0.61 g (4.10 mmol) of anhydrous zinc chloride[18] and a magnetic stirring bar was placed in an ice bath. Dry ether (1 mL) was added via syringe to the flask. To this solution was added via syringe under nitrogen flow 0.51 g (4.10 mmol) of *S*-methyl methanesulfonothioate (**12**) in 2 mL of dry ether. The solution was stirred 1 h at 0 °C, the reaction solution was washed with 15 mL of saturated ammonium chloride salution, and the organic layer was dried (Na_2SO_4). After removal of the solvent in vacuo, ^{1}H NMR showed only the presence of thiosulfonate **12**. No compounds were detected in the aqueous layer from the saturated ammonium chloride wash.

(48) Kurzer, F.; Powell, J. R. *J. Chem. Soc.* **1952**, 3728.
(49) Stirling, C. J. M. *Int. J. Sulfur Chem., Part B* **1971**, *6*, 277.

Attempted Reaction of Methanesulfinyl Chloride (2) with Anhydrous Zinc Chloride at 0 °C. A small amount of anhydrous zinc chloride[18] was added to a solution of methanesulfinyl chloride (**2**) in $CDCl_3$ in a 5-mm NMR tube. The ^{1}H NMR and ^{13}C NMR spectra were taken as soon as possible after addition. The ^{1}H NMR spectrum was taken again after the solution was kept at 22-24 °C for several hours. All spectra showed the presence of only methanesulfinyl chloride (**2**).

Stability of Methanesulfinyl Chloride (2) in the Absence of Activated Zinc. A solution of 2.96 g (30 mmol) of methanesulfinyl chloride (97.5% **2** and 2.5% **26**) in 12 mL of dry ether was syringed into a flame-dried, nitrogen-flushed, 25-mL, round-bottomed flask containing a magnetic stirring bar. After the solution was stirred for 1 h at 0 °C under dry nitrogen, the ether was removed in vacuo. Proton NMR analysis of the residue in $CDCl_3$ showed the presence of only methanesulfinyl chloride (**2**, 97.5%) and **26** (2.5%).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, to the National Science Foundation (Grant CHE-82-19149) for support of this research, and to the National Science Foundation for financial assistance toward the purchase of the NMR spectrometers.

Registry No. **2**, 676-85-7; **3**, 1718-44-1; **4**, 23267-68-7; **5**, 13455-88-4; **6**, 23267-70-1; **7**, 41892-39-1; **8**, 72394-49-1; **9**, 70936-25-3; **12**, 2949-92-0; **13**, 682-91-7; **14**, 1113-13-9; **15**, 1118-40-7; **16**, 78630-48-5; **17**, 88130-84-1; **18**, 7651-62-9; **19**, 37784-86-4; **25**, 19186-23-3; **26**, 124-63-0; **27**, 75-18-3; **28**, 13882-12-7; **29**, 14128-56-4; Zn, 7440-66-6.

Rotational Selectivity in Cyclobutene Ring Openings. Model Studies Directed toward a Synthesis of Verrucarin A

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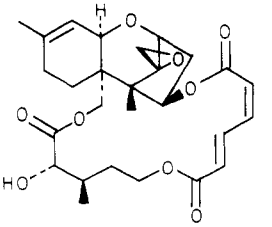
The rotational selectivity in the opening of dissymmetric cyclobutenes to the corresponding dienes is described. In the opening of the monoesters of *cis*-3,4-cyclobutenedicarboxylic acid, an unusual solvent effect on the ring opening is noted. Switching from Me_2SO to 1,2-dichloroethane leads to a 3:1 ratio of the (*E*,*Z*)-muconates, favoring the ester on the *E* double bond. The two isomers can be differentiated by ^{13}C NMR spectroscopy in which the above isomer shows a $\Delta\delta$ for the α,α' carbons of only $\sim$2.5 ppm but a $\Delta\delta$ of 5-6 ppm for the isomer having the ester on the *Z* double bond. Inclusion of the cyclobutene as part of a macrotriolide related to verrucarin A imparts conformational control on the rotational selectivity to favor the *E*,*Z* isomer corresponding to the natural products. These relatively simple models inhibit protein synthesis in a fashion reminiscent of the natural products.

Introduction

Verrucarin A is a representative example of a class of macrocyclic compounds, the macrocyclic trichothecanes, which display a wide array of biological activity including significant cytotoxicity.[1] Verrucarin A itself causes 50% inhibition of mouse tumor cell (P-815) growth at a concentration of 0.6 ng/mL, making it one of the most active cytostatic agents known.[2] As is usual with potent cytostatic agents, verrucarin A is also extremely toxic, possessing an LD_{50} (mouse) of 0.5 mg/kg (ip).[1c] Along with the verrucarins, the roridins and baccharins, both dilactides, comprise this important class of fungal metabolites. In all cases a macrocyclic "ribbon" joins the C-4 and C-15 hydroxy groups of a trichothecanoid backbone, most often



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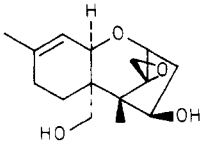

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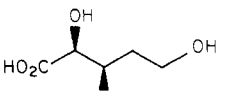

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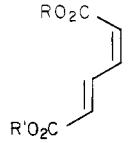

4

(1) Reviews: (a) Tamm, Ch. *Fortsch. Chem. Org. Naturst.* **1974**, *31*, 63. (b) Bamberg, J. R.; Strong, F. M. In "Microbial Toxins"; Kadis, S., Ed.; Academic Press: New York, 1973; Vol. 3, pp 207-292. (c) Doyle, T. W.; Bradner, W. T. In "Anticancer Agents Based on Natural Product Models"; Cassidy, J. M., Duros, J., Eds.; Academic Press: New York, 1980; Chapter 2.
(2) Harri, C.; Loeffler, W.; Sigg, H. P.; Stahelin, C.; Tamm, Ch.; Wressinger, D. *Helv. Chim. Acta* **1962**, *45*, 839.

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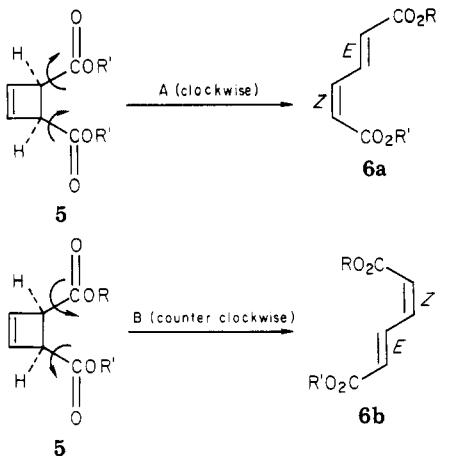
Scheme I



the diol verrucarol (2). Consonant with their biological activity and intriguing structure, the trichothecanes, both the simple sesquiterpenes and their macrocyclic derivatives, have been the focus of a number of synthetic studies[3] that have recently culminated in the synthesis of verrucarol[4] and the partial synthesis of verrucarin A.[5]

As with the previous syntheses of both verrucarin A[5] and some verrucarin model systems,[6] we planned to assemble the macrocycle via a series of esterifications. This strategy necessitated the construction of three separate pieces, verrucarol (2), verrucarinic acid (3), and an (*E,Z*)-muconate (4), which would subsequently be joined in a convergent manner to yield our target verrucarin A.[7] Having already described our successful solutions to both verrucarol[4b] and optically active verrucarinic acid derivatives,[8] we now report an approach to the solution of the (*E,Z*)-muconate moiety that may translate into an approach to the verrucarin family.

Vogel first demonstrated in 1954 that the (*E,Z*)-muconate structure was available through the thermal isomerization of *cis*-1,4-dicarboxycyclobutenes.[9] As later delineated by the rules of orbital symmetry,[10] these thermal valence isomerizations occur in a conrotatory fashion. In the case of a dissymmetric cyclobutene, two such conrotatory openings are possible, each yielding a different geometrical isomer as shown in Scheme I. Wanting to apply this methodology to the synthesis of the (*E,Z*)-muconate contained in the verrucarins, we had to find a control element that would force a selection between path A and path B.[11]

Table I. Effect of Solvents on the Thermal Openings of Half-Esters 7 and 8

cyclobutene	solvent (temp, °C)	diene ratio
7 (R = *n*-Bu)	Me_2SO (110)	10a:10b, 50:50
7	DME (85)	10a:10b, 55:45
7	$ClCH_2CH_2Cl$ (83)	10a:10b, 75:25
8 (R = $CH_2Cl_2Si(CH_3)_3$)	Me_2SO (85)	11a:11b, 55:45
8	$ClCH_2CH_2Cl$ (83)	11a:11b, 75:25
8	CCl_4 (76)	11a:11b, 75:25

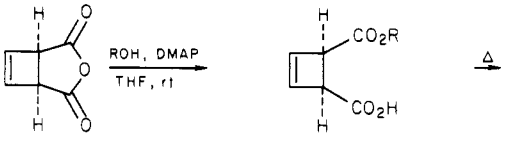
We envisioned two possible control elements. The first was to adjust the steric bulk of the two substituents (R and R′, Scheme I) so that the large group might prefer to swing away from the cyclobutene and therefore reside on the *E* olefin.[12]

An alternative control element considers the effect of a conformational constraint imposed by incorporating the cyclobutene into medium or large rings.[13] While simply substituted macrocycles would not be expected to show much selectivity, highly dissymmetric macrocycles could impose their conformational biases on the nature of the ring-opening process. During the course of these studies, the validity of the assumption of poor selectivity for simple systems was demonstrated.[11f] However, the relative conformational rigidity apparently associated with verrucarin A and the enhanced stability of the natural *E,Z* isomer compared with the alternative as predicted by molecular mechanics calculations would seemingly impose these factors onto this conrotatory process. The ability of a relatively simple dissymmetric macrotriolide to achieve such selectivity is an appealing question.

In this paper, we report the effects of these two approaches on the rotational selectivity in the opening of cyclobutenes. In addition, we have found that ^{13}C NMR spectroscopy represents a flexible and simple method to determine the stereochemistry of unsymmetrical (*E,Z*)-muconate monoesters. Biological evaluation of these simple models show suprising activity.

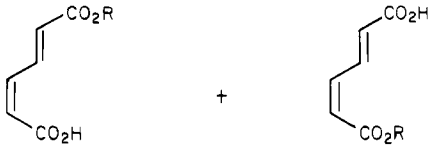
Opening of Dissymmetric Cyclobutenes

Although a number of dissymmetric *cis*-1,4-disubstituted-cyclobutenes[11] have been thermalized to yield in most cases mixtures of *E,Z* isomers, no studies existed on dissymmetric systems such as 5. Cyclobutenes 7 and 8



9

7, R = *n*-Bu
8, R = $(CH_2)_2Si(CH_3)_3$



10a, R = *n*-Bu
11a, R = $(CH_2)_2Si(CH_3)_3$

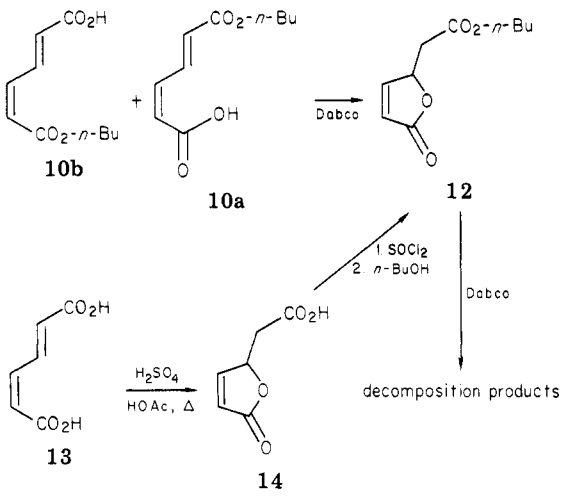
10b, R = *n*-Bu
11b, R = $(CH_2)_2Si(CH_3)_3$

were synthesized from the known anhydride 9 in order to initiate some preliminary studies in this area.[14] Not surprisingly, the anhydride 9 proved to be an excellent

(3) For reviews, see: (a) Ong, C. W. *Heterocycles* **1982**, *19*, 1685. (b) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *15*, 388.
(4) (a) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. (b) Trost, B. M.; McDougal, P. G. *Ibid.* **1982**, *104*, 6110.
(5) (a) Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242. (b) Mohr, P.; Tori, M.; Grossen, P.; Herold, P.; Tamm, Ch. *Helv. Chim. Acta* **1982**, *65*, 1412.
(6) (a) Breitenstein, W.; Tamm, Ch. *Helv. Chim. Acta* **1978**, *61*, 1975. (b) Notegen, E.-A.; Tori, M.; Tamm, C. *Helv. Chim. Acta* **1981**, *64*, 316.
(7) Not surprisingly these same three compounds are obtained from basic hydrolysis of verrucarin A, see: Gutzwiller, J.; Tamm, C. *Helv. Chim. Acta* **1965**, *48*, 157.
(8) Trost, B. M.; McDougal, P. G. *Tetrahedron Lett.*, submitted for publication.
(9) Vogel, E. *Angew. Chem.* **1954**, *66*, 640.
(10) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim/Bergstr., Germany; Academic Press: New York, 1970.
(11) A few examples of dissymmetric *cis*-1,4-disubstituted cyclobutene ring openings exist, see: (a) Gil-Av, E.; Shabatai, J. *J. Org. Chem.* **1964**, *29*, 257. (b) Pomerantz, M.; Hartman, P. H. *Tetrahedron Lett.* **1968**, 991. (c) Maier, G.; Wiebler, M. *Ibid.* **1969**, 4987. (d) Scharf, H.; Mattay, J. *Liebigs Ann. Chem.* **1977**, 772. (e) Kirmse, W.; Scheidt, F.; Vater, H. J. *J. Am. Chem. Soc.* **1978**, *100*, 3945. (f) Dauben, W. G.; Michno, D. M. *Ibid.* **1981**, *103*, 2284.
(12) For some precedent, see ref 11a,b.
(13) Egan, R. S.; Martin, J. R.; Perun, T. J.; Mitscher, L. A. *J. Am. Chem. Soc.* **1975**, *97*, 4578.
(14) Hartmann, W. *Chem. Ber.* **1969**, *102*, 3974.

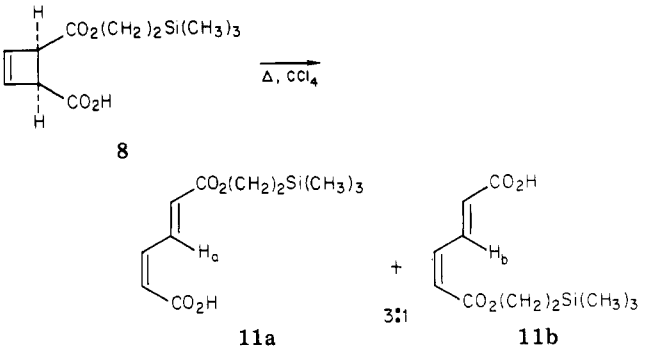
acylating agent and upon reaction with the appropriate alcohol and (dimethylamino)pyridine (DMAP) yielded the desired half-esters **7** and **8** in 95% and 87% yields, respectively. These cyclobutenes were thermally isomerized under a variety of conditions as summarized in Table I. Thermolysis of **7** in dimethyl sulfoxide (Me_2SO) at 110 °C resulted in approximately a 50:50 mixture of the *E,Z* isomers **10a** and **10b**. Although lowering the temperature and changing the solvent to dimethoxyethane had little effect on the isomer ratio, switching the solvent to dichloroethane caused a significant increase in the isomer **10a**.[15] Similar results were found with half-ester **8**; that is, in the chlorohydrocarbon solvents the diene **11a** with the ester group on the *E* olefin predominated. Qualitatively, the results can be rationalized purely on a steric argument. In solvents not capable of hydrogen bonding, the carbalkoxy and carboxy groups have similar steric requirements, leading to an equal mixture of diene isomers. In solvents capable of hydrogen bonding to the organic acid, the effective bulk of this substituent increases, due to the shell of solvent molecules clustered about it, and hence a higher percentage of the product would contain the carboxy group on the *E* olefin (25% in CCl_4, 50% in Me_2SO). An alternative explanation could be based on secondary orbital interactions. The nature and geometry of substituents at any reacting center effect the outcome of a reaction at least in part due to the manner in which they interact and distort the orbitals at that reacting center.[16,17] Since the extent and direction of the orbital distortion depends on the ground-state geometry, one would simply have to presume the cyclobutene conformation is different in Me_2SO and CCl_4, not unreasonable considering the hydrogen-bonding capabilities of the two solvents, to explain the difference in isomer ratio between the two solvents.

Initially, our assignment of stereochemistry was based on the chemical reactivity of the muconate isomers **10a** and **10b**. It was found that heating a 50:50 mixture of the isomers to 65 °C in Me_2SO containing 0.3 mol equiv of 1,4-diazabicyclo[2.2.2]octane (Dabco) caused the selection destruction of one of the two isomers over a period of 6 h. It was immediately suspected that the isomer **10a** had cyclized via an intramolecular Michael reaction to form the lactone **12**. This lactone was presumed to be unstable to the reaction conditions as it was never observed even upon careful monitoring by NMR spectroscopy. Due to geometrical constraints the other isomer **10b**, which could be isolated and purified (mp 62–63 °C), did not undergo cyclization and subsequent decomposition. To garner support for this hypothesis, the lactone **12**, the supposed intermediate, was independently synthesized as shown[18,19] and submitted to the above reaction conditions (Dabco in Me_2SO, 65 °C). In agreement with our proposition, the lactone was completely consumed within 45 min, yielding no recognizable products. Literature precedent exists for both the intramolecular Michael addition[11d,18,19] and the



base lability of the resulting butenolides.[18,19] As will be seen, this selective destruction of one *E,Z* isomer proved useful in our model studies.

In order to further substantiate our assignments of the (*E,Z*)-muconate isomers, we contemplated an independent synthesis of one of the isomers. Fortunately, during the course of this work, Still and Ohmizu reported the synthesis of **11a** in connection with their synthesis of verrucarin A.[5a] We obtained this compound as the major isomer in the valence isomerization of **8**, and through repeated



recrystallizations it was possible to obtain a pure sample of **11a** (mp 68–69 °C).[5b,20] The ^1H NMR (270 MHz) spectrum of the purified material correspond perfectly to that reported by Still and Ohmizu. The most diagnostic proton was H_a (see structure **11a** above), which appeared at δ 8.35 with its characteristic coupling pattern (ddd, J = 15.6, 11.8, 0.9 Hz). In the isomeric (*E,Z*)-muconate **11b** this proton, H_b, resonates at δ 8.52 with the same coupling pattern as H_a.

During the course of our studies, we also found that ^{13}C NMR shifts could be used to assign stereochemistry in (*E,Z*)-muconate isomers. The most informative shifts, as shown in Table II,[24] are those for the two carbons α to the carbonyl groups, referred to as the α and α' carbons. It can be seen from the spectra that when this carbon is contained in the *E* olefin, it appears 4-ppm downfield from

(15) Similar to other concerted processes, the cyclobutene openings are subject to charge assistance. For example, dicarboxylates related to **5** (R, R′ = Na) have been shown to open below room temperature (see ref 11d). Similar behavior is seen in benzocyclobutanoxides (see ref 49) where the anion is vicinal to the reacting center in direct analogy to the oxy-Cope rearrangement. Unfortunately, we have not been able to utilize this observation as the carboxylate salts of our compounds show some isomerization prior to ring opening yielding *E,E*-dienes.

(16) For a general description of orbital distortion, see: Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703.

(17) For a brief treatise on the applicability of secondary orbital interactions in cyclobutene openings, see ref 11f.

(18) Elvidge, J. A.; Linstead, R. P.; Orkin, B. A.; Sims, P.; Baer, H.; Pattison, D. B. *J. Chem. Soc.* **1950**, 2228.

(19) Elvidge, J. A.; Linstead, R. P.; Sims, P.; Orkin, B. A. *J. Chem. Soc.* **1950**, 2235.

(20) Vogel, E. *Liebigs Ann. Chem.* **1958**, *615*, 14.

(21) Maciel, G. E.; Ellis, P. D.; Nattersand, J. J.; Savitsky, G. B. *J. Magn. Reson.* **1969**, *1*, 589.

(22) Solvent effects on the α-carbon shifts of acrylic esters have been shown to be negligible (ref 21). Acids, however, are particularly prone to solvent shifts (ref 23), although no study has shown what effect solvent might have on the shift of the α carbon in acrylic acids.

(23) Maciel, G. E.; Traficante, D. D. *J. Am. Chem. Soc.* **1966**, *88*, 220.

(24) The compounds in entries 2 and 3 were prepared by photolysis of the corresponding *E,Z* isomers in the presence of iodine (ref 18). For preparation of entry 3, see Experimental Section.

Scheme II

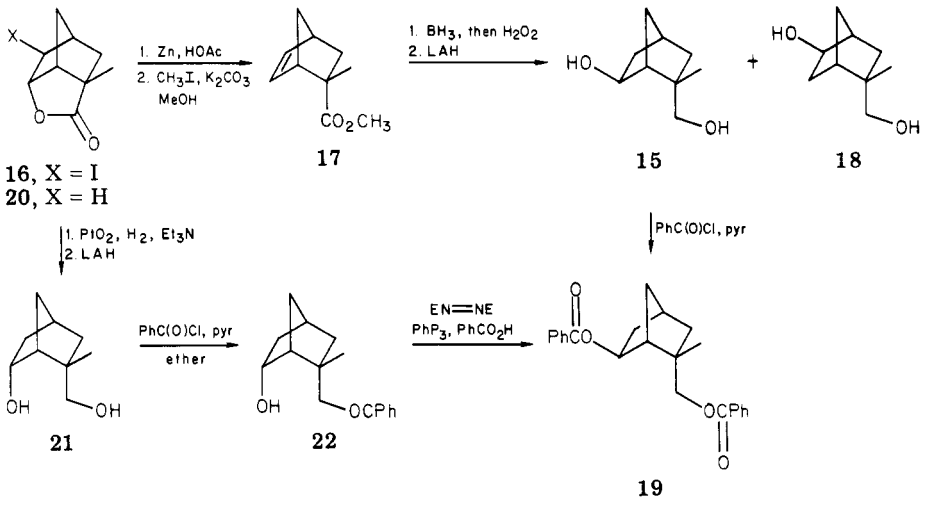


Table II. ^{13}C NMR Shifts of (*E*,*Z*)-Muconate Isomers[d]

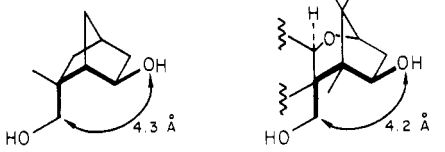
entry	compd	HC=CC=O	HC= CC=O	HC=CC=O	$\Delta^{\alpha,\alpha'}$ [e]
1	13	166.9 Ea	139.9	129.4 Ea	4.0
		166.4 Za	138.1	125.4 Za	
2	(*E*,*E*)-13	166.9 Ea	140.6	129.4 Ea	
3	(*E*,*E*)-10	166.6 Ea	141.1	129.6 Ea	2.0
		165.2 Ee	140.3	127.6 Ee	
4[c]	10b	166.8 Ea	140.7	130.1 Ea	6.2
		164.9 Ze	137.7	123.9 Ze	
5[b]	11b	166.4 Ea	140.4	129.8 Ea	6.0
		164.5 Ze	137.5	123.8 Ze	
6	30	163.6 Ea	137.8	127.6 Ea	5.3
		164.4 Ze	135.3	122.3 Ze	
7[a]	10a	166.3 Za	139.6	128.1 Ee	2.3
		165.5 Ee	138.4	125.8 Za	
8[b]	11a	165.9 Za	139.5	128.1 Ee	2.6
		165.2 Ee	138.0	125.5 Za	

[a] Data obtained from a spectrum containing the mixture of isomers. [b] Data obtained from a spectrum containing a 3:1 mixture of isomers. [c] Data obtained from an isomerically pure sample. [d] The letters following the chemical shift indicate which carbon is assigned to that shift. E and Z refer to the olefin geometry and a and e refer to whether the assigned carbon resides on the acid or ester portion of the muconate. [e] $\Delta^{\alpha,\alpha'}$ is the difference in chemical shift between the carbons α to the carbonyl group.

the corresponding carbon in the *Z* olefin (entry 1). This correlates well with the trend observed in maleates and fumarates,[21] where the fumarate derivatives (*E* olefin) are 4–5-ppm downfield relative to the maleates (*Z* olefin). Furthermore, in the muconate half-esters the carbon α to the acid is approximately 2-ppm downfield relative to the carbon α to the ester, assuming both are in the same geometrical environment (entry 3). The sum of these effects makes the value for $\Delta^{\alpha,\alpha'}$, as defined in Table II, diagnostic of isomer geometry in (*E*,*Z*)-muconic acid half-esters. The spectra of the isomers in which the acid moiety resides on the *E* olefin record a $\Delta^{\alpha,\alpha'}$ value of approximately 5–6 ppm (entries 4, 5, and 6), while for the isomers in which the ester group is on the *E* olefin this value is about 2.5 ppm. It should be noted that in our study the ^{13}C spectra were obtained in Me_2SO-d_6, used for its solubility properties, and therefore care should be exercised in extending this correlation to spectra obtained in other solvents.[22]

Synthesis of a Verrucarol Model Diol

We were primarily interested in designing a molecular mimic for the verrucarol portion due to the limited supply of verrucarol itself.[25] Inspection of molecular models



15 verrucarol (1)

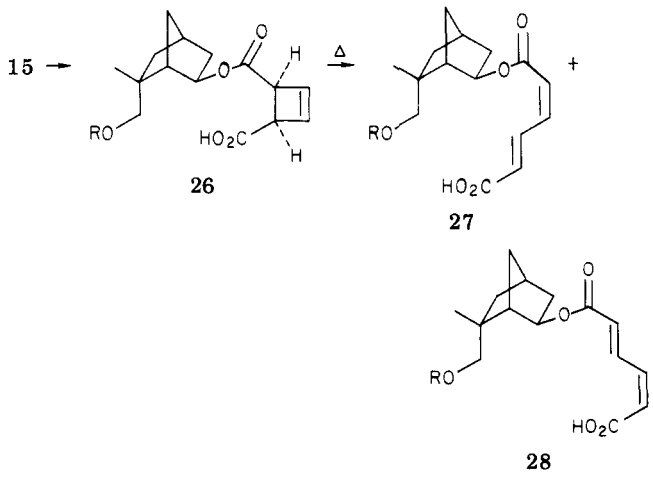
reveals that both the orientation of the key bonds (darker bonds in the above structures) and the distance between the oxygen of the secondary alcohol and the carbon of the hydroxymethyl group are nearly identical for diol **15** and verrucarol. One element missing in **15** was a bridgehead methyl group corresponding to the C-14 methyl group in verrucarol. This group was not considered essential to the model study and was ignored due to the synthetic complications its inclusion would accrue.

The synthesis of the verrucarol model, shown in Scheme II, began with the known iodo lactone **16**,[26] a compound arising from the Diels–Alder reaction of cyclopentadiene and methyl methacrylate.[27] Reductive elimination of the iodo lactone followed by esterification gave the olefin **17** in 74% yield. Hydroboration with subsequent oxidation occurred stereospecifically on the exo face of the olefin[28] but gave a 60:40 mixture of alcohol isomers. This mixture was reduced with lithium aluminum hydride to give the diols **15** and **18** as an oily solid with **15** predominating. One recrystallization from chloroform–hexane yielded a solid greatly enriched (~85%) in the desired regioisomer **15**. Two more recrystallizations yielded our model diol **15** in pure form (mp 119.5–121 °C). Even with the repeated recrystallizations, the yield of pure diol from the olefin **17** was 26%, so that 5 g of diol was easily prepared by this route. In order to prove that we had indeed purified the desired regioisomer, the dibenzoate derivative **19** was prepared by an independent route. Hydrogenolysis of the iodide (89%) to the lactone **20** followed by lithium aluminum hydride reduction (99%) furnished the diol **21**.

(25) At the time that our work was initiated, the principal source of verrucarol was via base hydrolysis of verrucarin A (ref 7). Since then a route to verrucarol from the more readily available trichothecane anguidine has been described, see: Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.* **1980**, *21*, 4549.

(26) Beckmann, S.; Geiger, H. *Chem. Ber.* **1961**, *94*, 48.
(27) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 2032.
(28) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 2544.

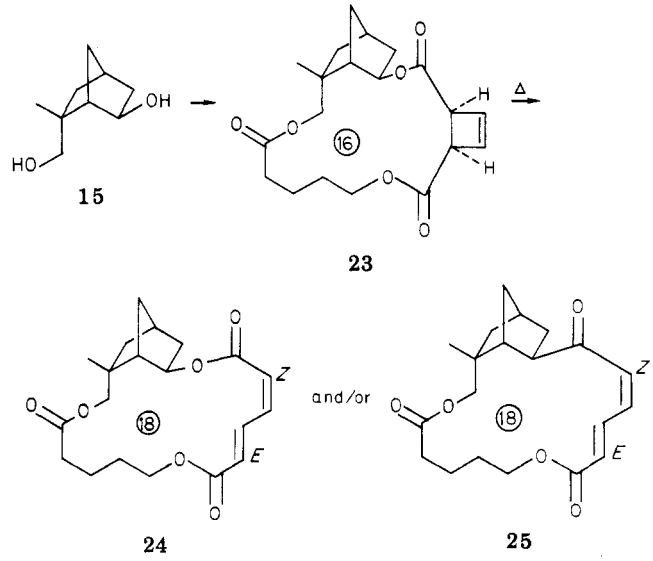
Scheme III



Treatment with 1 equiv of benzoyl chloride and pyridine in ether yielded the primary benzoate **22** in 47% yield along with 22% of the secondary monobenzoate. Inversion of the secondary alcohol via diethyl azodicarboxylate methodology[29] yielded the inverted dibenzoate **19** (mp 111–112 °C). This reaction was accompanied by substantial amounts of elimination to olefin and formation of noninverted dibenzoate.[30] None the less, the desired dibenzoate **19** was identical in all respects, including mixed melting point, with the dibenzoate prepared from the purified diol **15**.

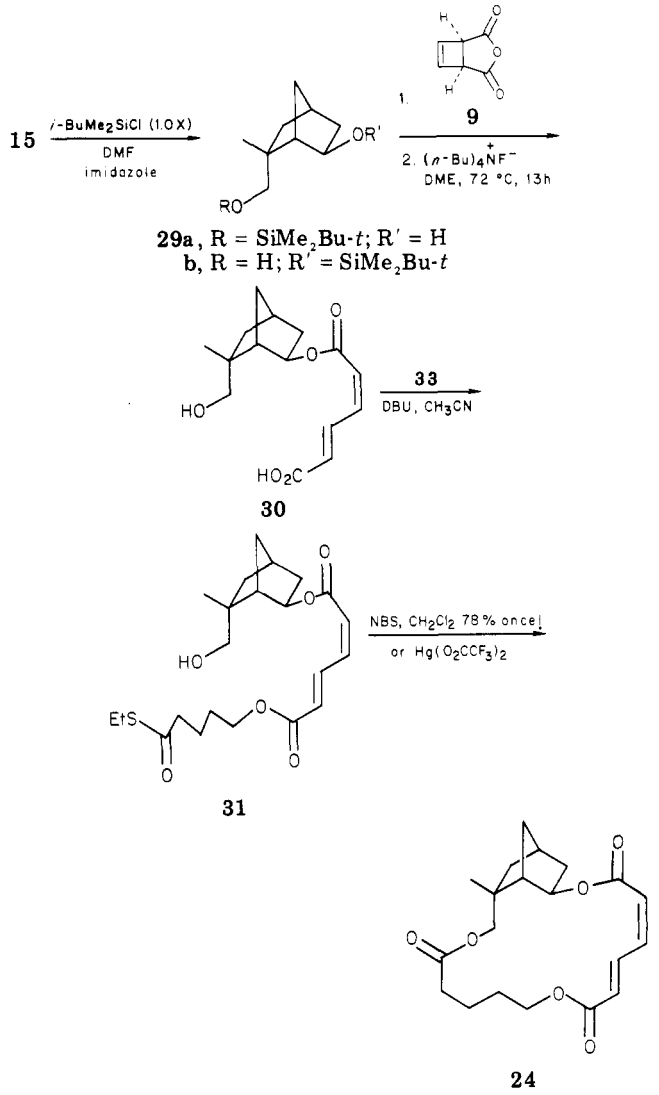
Syntheses of Verrucarin A Model Macrocycle

With our model diol **15** in hand, we initiated the synthesis of the macrocycle **23**. Inspection of the isomers **24** and **25** that would result upon thermolysis of **23** revealed



that their structures would be difficult to distinguish by conventional spectroscopic methods. Therefore, before we could proceed with this line of research, we needed to effect an independent synthesis of either **24** or **25**. The "natural" model system **24** was chosen for synthesis as the knowledge garnered during its synthesis might prove useful in the transformation of verrucarol to verrucarin A.

Scheme IV

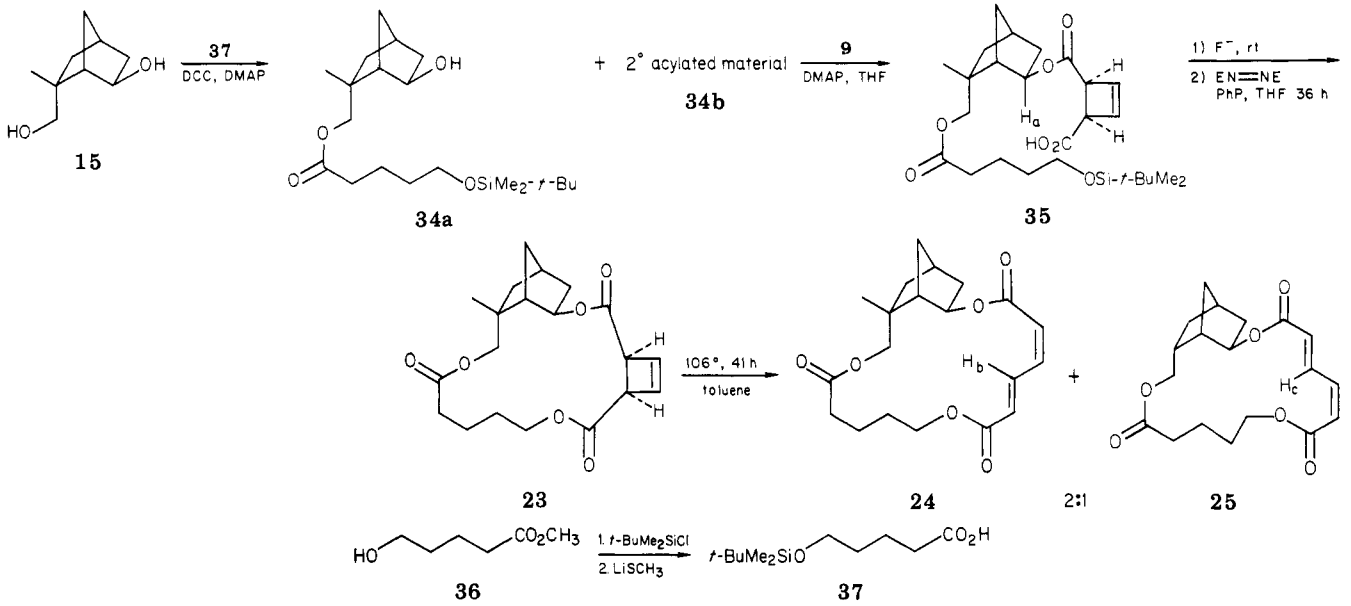


Our plan for the synthesis of **24**, which incorporates the "selective destruction" concept, is shown in Scheme III. Heating the cyclobutene **26** in a solvent capable of hydrogen bonding would be expected, from our previous results, to yield a 50:50 mixture of *E,Z* isomers. Treatment of this mixture with base would then cause the unwanted *E,Z* isomer, with its carboxy group capable of undergoing an intramolecular cyclization, to self-destruct, leaving only the desired *E,Z* diene **27** to be isolated. This compound could then be carried onto the desired macrocyclic diene **24** in a fashion that would allow for the unambiguous assignment of *E,Z*-geometry.

Our synthesis (Scheme IV) began with the attempted selective protection of diol **15**. Silylation with *tert*-butyldimethylsilyl chloride gave a 2:1 mixture of monosilylated compounds with the secondary silylated compound **29b** predominating. Even employment of methylene chloride with DMAP as base, conditions purported to select for primary alcohols,[32] gave predominantely **29b**. As we were most interested in the chemistry yet to come, the poor chemoselectivity demonstrated by the diol was accepted and the silyl alcohol **29a** carried on. Acylation

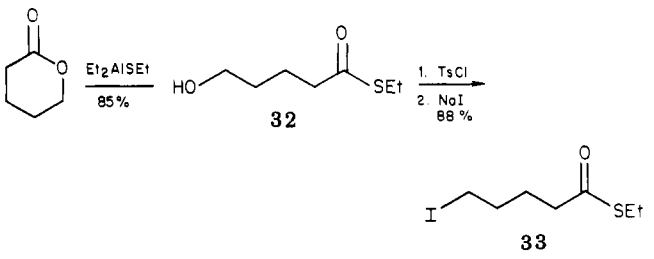
(29) For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1.
(30) Attempts to invert the corresponding tosylate from **21** with potassium superoxide and 18-crown-6 proved futile. This tosylate did yield inverted products upon reaction with tetra-*n*-butylammonium formate or cesium propionate (ref 31).
(31) Kruizinga, W. H.; Shijtveen, B.; Kellog, R. M. *J. Org. Chem.* **1981**, *46*, 4321.
(32) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

Scheme V



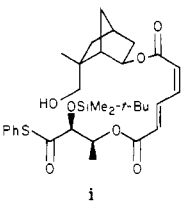
with the anhydride **9** proceeded smoothly (DMAP, THF) to yield the cyclobutene **26** [R = $SiMe_2Bu$-*t*] as a mixture of diastereomers (only one diastereomer is drawn). Without purification, the compound was treated with tetra-*n*-butylammonium fluoride in DME at 72 °C, which simultaneously removed the silyl protecting group, opened the cyclobutene ring to a mixture of dienes, and catalyzed the decomposition of the base labile *E,Z* isomer **28** (R = H). The desired diene **30** was isolated in a yield of 39% from **29a** (maximum anticipated yield 50%). Its structure is based not only on mechanistic considerations, that is destruction of the isomeric *E,Z* compound via fluoride-catalyzed Michael cyclization,[33] but also on its ^{13}C NMR spectrum, which recorded a $\Delta^{\alpha,\alpha'}$ value of 5.2 ppm, indicative of the assigned stereochemistry (see Table II). The hydroxy acid **30** was an unstable solid [mp 125.5–129 °C dec] prone to polymerization even when stored at 0 °C.

To complete the synthesis of the macrocycle **24**, a number of reactions were investigated to functionalize **30** with a five-carbon hydroxy acid. Initial attempts to either acylate the primary alcohol with an acid chloride or to esterify the acid with the alcohol **32** met with failure, presumably in part due to the instability of the starting hydroxy acid. Hypothesizing that the carboxylate salt of **30** was stable, as evidenced by the conditions for its formation, we attempted an alkylative esterification with the primary iodide **33** prepared from δ-valerolactone as shown.



Using the recently published conditions (DBU, CH_3CN)[34] for such reactions a 58% yield of the thioester **31** was realized. A minor drawback to this procedure was the formation of small amounts (~5%) of the corresponding *E,E* isomer as evidenced by complex multiplets at δ 6.21 and 7.3 in the NMR spectrum.[42] As will be seen, this isomer does not affect the completion of the synthesis as it is unreactive toward macrolactonization.

With the obtention of the thioester we were ready to attempt macrolactonization. Aryl- and *tert*-butyl thioesters, especially in consort with metal cations, have been used extensively as activating groups for lactone formation.[35,36] Activation of the ethyl thioester for lactonization with NBS[37] was explored. Stirring the thioester with 7.5 equiv of NBS in methylene chloride (4×10^{-3} M in **31**) at room temperature in the dark for 18 h led to the isolation of the desired lactone **24** in 78% yield based on recovered starting material. The product was clearly one *E,Z* isomer, and the mass spectrum (M^+ *m/e* 362) confirmed the formation of monomer. Unfortunately, this reaction proved capricious, especially upon attempted scale-up. The lactone could be obtained with mercuric trifluoroacetate in acetonitrile although the yield was low (29%) due to concomitant isomerization of the starting material to the



i

(33) For a review of fluoride-catalyzed reactions, see: Clark, J. H. *Chem. Rev.* **1980**, 429.
(34) Rao, C. G. *Org. Prep. Proced. Int.* **1980**, *12*, 225.
(35) For reviews, see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23.
(36) Rastetter, W. H.; Phillion, D. P. *Tetrahedron Lett.* **1979**, 1469.
(37) Kumamoto, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2111. Minato, H.; Takeda, K.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 1095.
(38) For similar observations in other verrucarin-type cyclizations, see ref 5 (verrucarin A) and ref 6a (tetrahydroverrucarin J).
(39) Attempted cyclizations of i under a variety of conditions yielded no lactonic products.
(40) Demethylation of the ester in the presence of the silyl protecting group with lithium mercaptide (ref 41) is noteworthy.
(41) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859.
(42) In general (*E,E*)-muconates and (*E,Z*)-muconates are easily distinguished by ^1H NMR. The *E,E* compounds record complex multiplets at approximately δ 6.2 and 7.3 assigned as the α,α' and β,β' protons, repsectively. In the *E,Z* isomers the β,β' protons are grossly anisochronous and hence appear as two distinct patterns at approximately δ 8.0 and 6.6.

E,E diene. Evidently this isomer is incapable of lactonizing as none of the *E,E* macrocycle was detected.[38,39]

With the successful synthesis of the diene **24**, the thermal isomerization of the macrocyclic cyclobutene **23** could now be studied. Esterification of the diol with 1 equiv of the acid **37** (DCC, DMAP), whose synthesis is described in Scheme V,[40] gave a 3:1 mixture of the monoacylated alcohols **34a** and **34b** with the desired primary acyl product predominant. Separation of the products was partially achieved by use of HPLC in which case the pure ester **34a** was isolated in a 33% yield. Acylation with the anhydride **13** (98%) gave **35** as a mixture of diastereoisomers clearly distinguishable by ^{1}H NMR (270 MHz) spectroscopy, which showed signals for H_a (see structure **35**) at δ 4.89 and 4.92 (both bd, J = 6.1 Hz). That these signals were not due to cis and trans isomers of the cyclobutene was evident from thermolysis of the lactone **23**, which yielded only *E,Z* dienes as will be described. Desilylation was accomplished with tetra-*n*-butylammonium fluoride at room temperature for 3 h, and the crude secohydroxy acid was then cyclized by the procedure of Mitsunobu[29] to yield the desired macrocycle **23** in 71% yield from **35**. Cyclization at this position of the macrocycle is clearly more efficient that those performed in the synthesis of **24**.[5]

Having the key macrocycle in hand, the cyclobutene was thermolyzed with great anticipation. It was found that temperatures of 106 °C were needed to effect the desired valence isomerization. After 41 h at this temperature, the cyclobutene had completely opened, yielding a 2:1 mixture of *E,Z* dienes, easily separable by chromatography. The major isomer was identical by ^{1}H NMR (270 MHz) and mass spectroscopy and analytical TLC with the previously synthesized *E,Z* macrocycle, unambiguously assigned as isomer **24**. In particular, the major isomer has a signal (H_b) at δ 8.27 (ddd, J = 15.5, 11.0, 12.3 Hz), while the minor isomer records a similar pattern (H_c) at δ 7.80. That both compounds were monomers from the secoacid **35** was evident from the mass spectra in which parent ions were observed at m/e 362. This result is indeed exciting and one that bodes well for the synthesis of verrucarin A.

Conclusion

Our studies to date have demonstrated that dissymmetric *cis*-1,4-disubstituted-cyclobutenes can be forced to select, at least partially, between the two possible conrotatory openings it has at its disposal. Particularly engrossing is the isomerization of the macrocyclic cyclobutene **23**, which shows a propensity to form the *E,Z* isomer related to the verrucarin skeleton. It is our belief that as one constructs systems which more closely resemble the natural product, an even more striking rotational selectivity will be seen.

In light of the current interest in the biological activity of the trichothecanes[1] both *E,Z* isomers **24** and **25** were tested for their ability to inhibit protein synthesis.[43] When these compounds were incubated with intact H–HeLa cells in the presence of L-[4,5-$^3H_2$]leucine, they were found to inhibit leucine uptake by 62% and 50% relative to the control at a concentration of 30 μg/mL.[44] Interestingly, it is the unnatural *E,Z* isomer **28**, that expressed the somewhat higher activity. Although this activity is approximately one-third that of anguidine and its analogues,[45] they are, to our knowledge, the first trichothecane-like analogues minus the 12,13-epoxide that exhibit such behavior.

General Methods

All reactions were run under a positive pressure of dry nitrogen. Reactions requiring anhydrous conditions were performed in flame-dried glassware that was cooled under nitrogen. Solvents were distilled before use: hexamethylphosphoric triamide (HMPA), methylene chloride, 1,2-dichloroethane, pyridine, hexane, and pentane from calcium hydride; tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) from sodium benzophenone ketyl; acetic acid and ethyl acetate were collected after a large forerun was discarded. Cases where the extraction solvent is listed as solvent (2 × volume) indicates that two separatory funnels were used in series so that every aqueous wash is back-extracted with the indicated organic solvent. The term in vacuo refers to solvent removal via a Büchi rotoevaporator at water aspirator pressure, followed by evacuation of the flask at ~0.5 mm for several hours. Preparative thin-layer chromatography was performed on glass plates coated with 1.5 mm of silica gel (Machery-Nagel, MN-Kieselgel, P/UV$_{254}$). Column chromatography was performed on silica gel from W.R. Grace (grade 62, 60–200 mesh). Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters Prep 500A instrument using a PrePak-500 cartridge. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a JEOLCO MH-100 or a Bruker WH-270 instrument. Chemical shifts are reported in δ units, parts per million (ppm), downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Infrared spectra (IR) were determined in the indicated solvent in sodium chloride cavity cells on a Perkin-Elmer 267 or a Beckman Acculab 7 spectrometer. Certain peak shapes are indicated as sh, sharp; br, broad. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were determined on a JEOLCO FX-60 (15.04 MHz) spectrometer, and the chemical shifts (δ units) are reported downfield from tetramethylsilane. Mass spectra (MS) were obtained on an AEI-902 instrument at an ionizing current of 98 mA with an ionizing voltage of 70 eV. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI, or Galbraith Laboratories, Knoxville, TN.

***cis*-3-(*n*-Butoxycarbonyl)-4-carboxy-1-cyclobutene (7).** To 1-butanol (0.358 g, 4.84 mmol) in DME (5 mL) was added anhydride **9** (0.5 g, 4.03 mmol), pyridine (0.474 g, 6.0 mmol) and DMAP (0.1 g, 0.82 mmol). The reaction was stirred at room temperature for 2 h, diluted with ethyl acetate (100 mL), washed with 5% aqueous hydrochloric acid (2 × 20 mL) and saturated aqueous sodium chloride (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was passed through Florisil (3 × 15 cm) with 50% ethyl acetate–hexane containing 0.5% formic acid to yield **7** (0.758 g, 95%) as a colorless oil: IR ($CHCl_3$) 3400–2900 (br), 1735–1705 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.0 Hz), 1.2–1.76 (4 H, m), 3.97 (2 H, s), 4.13 (2 H, t, J = 7.0 Hz), 6.30 (2 H, s), 11.0 (1 H, s); ^{13}C NMR (Me_2SO-d_6) δ, 171.5, 170.0, 137.0, 136.2, 63.7, 48.9, 48.3, 30.1, 18.6, 13.5; MS, m/e (relative intensity) 198 (0.8), 125 (68), 98 (39), 97 (97), 57 (69), 41 (100); calcd for $C_{10}H_{14}O_4$ 198.0893, found 198.0894.

***cis*-3-[[2-(Trimethylsilyl)ethoxy]carbonyl]-4-carboxy-1-cyclobutene (8).** To 2-(trimethylsilyl)ethanol (0.628 g, 5.25 mmol) in THF was added anhydride **9** (0.60 g, 4.84 mmol) along with DMAP (0.742 g, 6.06 mmol). The reaction was stirred for 18 h at room temperature to yield a brownish solution with a small amount of precipitate. The mixture was diluted with 50% ether–ethyl acetate (200 mL), washed with 10% aqueous copper sulfate (2 × 30 mL), 10% aqueous ammonium chloride (20 mL), dried ($MgSO_4$), treated with Norite, filtered, and concentrated in vacuo to yield an oil, which crystallized upon standing. Recrystallization from hexane (–20 °C) yielded the product **8** (1.02 g, 87%) as a white powder: mp 54.5–55.5 °C; IR (CCl_4) 3330–2900 (br), 1748, 1722 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (9 H,

(43) Ueno, Y.; Hosoya, M.; Morita, Y.; Ueno, I.; Tatsuno, T. *J. Biochem. (Tokyo)* **1968**, *64*, 479.

(44) Dr. Eric Cundliffe, unpublished work in the laboratories of Dr. Julian Davies.

(45) Cundliffe, E.; Davies, J. E. *Antimicrob. Agents Chemother.* **1977**, 491. Kaneko, T.; Schmitz, H.; Essery, J. M.; Rose, W.; Howell, H. F.; O'Herron, F. A.; Nachfolger, S.; Huftalen, J.; Bradner, W. T.; Partyka, R. A.; Doyle, T. W.; Davies, J.; Cundliffe, E. *J. Med. Chem.* **1982**, *25*, 579.

s), 0.98 (2 H, m), 3.93 (2 H, s), 4.31 (2 H, m), 6.25 (1 H, d (AB), J = 3 Hz), 6.29 (1 H, d (AB), J = 3 Hz); MS, m/e (relative intensity) 199 (16.3) 169 (16.4), 97 (16.0), 75 (100), 73 (94.2); calcd for $C_{11}H_{18}O_4$ 214.1206, found 214.1205.

1-(*n*-Butoxycarbonyl)-4-carboxy-1,3-(*Z*,*E*)-butadiene (10b). Cyclobutene **7** (110 mg, 0.505 mmol) was dissolved in Me_2SO-d_6 (0.75 mL), placed in an NMR tube and heated at 110 °C for 1.2 h. Analysis by ^1H and ^{13}C NMR showed a 1:1 mixture of the two *E*,*Z* isomers **10a** and **10b**. To this mixture was added 1,4-diazabicyclo[2.2.2]octane (20 mg, 0.178 mmol). The NMR tube was placed in an oil bath at 65 °C. Analysis by ^1H NMR (100 MHz) showed the slow disappearance of one isomer, and after 6 h only one isomer remained. The reaction was diluted with ether and extracted twice with 10% aqueous sodium carbonate (30 mL). The base washes were combined, acidified with 10% aqueous sulfuric acid at 0 °C, and extracted with ethyl acetate (2 × 30 mL). The ethyl acetate was dried ($MgSO_4$), concentrated in vacuo, and placed under a high vacuum (0.1 mm) for 12 h to yield a tannish solid (65 mg, 59%), which was nearly pure **10b**. The solid was dissolved in 10% aqueous potassium carbonate (50 mL) and neutralized with concentrated hydrochloric acid at 0 °C. A white flaky solid resulted, which was collected by filtration and dried under high vacuum (0.1 mm) to yield pure **10b** (42 mg, 38%): mp 62–64 °C; IR ($CDCl_3$) 3400–2900, 1712, 1700, 1637, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (3 H, t, J = 6.5 Hz), 1.18–1.84 (4 H, m), 4.24 (2 H, t, J = 6.5 Hz), 5.90 (1 H, d, J = 11.0 Hz), 6.12 (1 H, d, J = 15.0 Hz), 6.62 (1 H, t, J = 11.0 Hz), 8.42 (1 H, dd, J = 15.0, 11.0 Hz), 6.62 (1 H, t, J = 11.0 Hz), 8.42 (1 H, dd, J = 15.0, 11.0 Hz); ^{13}C NMR (Me_2SO-d_6) δ 166.8, 164.9, 140.7, 137.7, 130.1, 123.9, 63.8, 30.1, 18.6, 13.4; MS, m/e (relative intensity) 198 (0.7), 125 (34.1), 101 (36.2), 97 (100.0), 56 (71.8), 55 (32.9), 43 (40.2); calcd for $C_{10}H_{14}O_6$ 198.0892, found 198.0886.

4-(*n*-Butoxycarbonyl)-1-carboxy-1,3-(*E*,*Z*)-butadiene (10a and 10b) (3:1 Mixture from Thermolysis in 1,2-Dichloroethane). The cyclobutene **7** (72 mg, 0.36 mmol) was refluxed in 1,2-dichloroethane (2 mL, bp 83 °C) for 17 h. Removal of the solvent in vacuo left a pale yellow oil (73 mg). **10a** and **10b**: ^1H NMR (100 MHz, $CDCl_3$) δ 0.94 (3 H, t, J = 6.5 Hz), 1.18–1.84 (4 H, m), 4.24 (2 H, t, J = 6.5 Hz), 5.90–6.29 (2 H, m), 6.62 and 6.72 (1 H, both t, J = 11.0 Hz), 8.32 and 8.42 (1 H, both dd, J = 16, 11.02 Hz).

The mixture was placed in THF (0.6 mL) and triethylamine (18.2 mg, 0.18 mmol) added. ^1H NMR (100 MHz) showed that the signals at δ 8.40 had separated by 0.4 ppm with the minor isomer **10b** appearing upfield. Integration showed a 3:1 mixture of isomers. When this mixture was refluxed, the signal for the major isomer **10a** slowly disappeared, until after 11 h only the minor isomer **10b** remained. ^{13}C NMR of **10a**: (data obtained from the spectrum of a 3:1 mixture of **10a** and **10b**) (Me_2SO-d_6) δ 166.8, 165.5, 139.6, 138.4, 128.1, 125.8, 63.8, 30.1, 18.6, 13.4.

1-(*n*-Butoxycarbonyl)-4-carboxy-1,3-(*E*,*E*)-butadiene (Entry 3, Table II). The pure *Z*,*E* isomer **10b** (62 mg, 0.313 mmol) in chloroform (0.6 mL) containing a crystal of iodine was photolyzed at room temperature with a 150-W bulb for 2 h. The reaction solution was poured into chloroform (60 mL), washed with 10% aqueous sodium thiosulfate, dried ($MgSO_4$), and concentrated in vacuo to yield the *E*,*E* isomer as a white solid (69 mg): mp 97–99 °C (not recrystallized) IR ($CHCl_3$) 1700 (br), 1640, 1615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3 H, t, J = 6.5 Hz), 1.44 (2 H, sextet, J = 6.5 Hz), 1.72 (2 H, pentet, J = 6.5 Hz), 4.22 (2 H, t, J = 6.5 Hz), 6.21 (1 H, d, J = 14.0 Hz), 7.35 (3 H, m); ^{13}C NMR (Me_2SO-d_6) δ 166.5, 165.2, 141.1, 140.3, 129.6, 127.6, 63.8, 30.0, 18.5, 13.4; MS, m/e (relative intensity) 198 (0.6), 143 (94.6), 125 (100), 97 (93.1), 56 (98.4); calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0853.

1-[[2-(Trimethylsilyl)ethoxy]carbonyl]-4-carboxy-1,3-(*E*,*Z*)-butadiene (11a) and 1-[[2-(Trimethylsilyl)ethoxy]carbonyl]-4-carboxy-1,3-(*Z*,*E*)-butadiene (11b). The cyclobutene **8** (575 mg, 2.37 mmol) was refluxed in carbon tetrachloride (6 mL, 76 °C) for 23 h. The solvent was removed in vacuo to yield a white solid (574 mg), which was shown by integration of the signals at δ 8.35 and 8.52 (vide infra) to be 73:27 mixture of the isomers **11a** and **11b** with **11a** predominating. A pure sample of the major isomer (97 mg, 17%) was obtained after three recrystallizations from ether–hexane at −20 °C. Pure **11a**: mp 68–69 °C (lit.[5b] mp 69–71 °C); IR (CCl_4) 3300–2850 (br), 1725, 1698, 1644, 1608 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (9 H, s), 0.99 (2 H, m), 4.23 (2 H, m), 5.97 (1 H, d, J = 11.8 Hz), 6.14 (1 H, d, J = 15.6 Hz), 6.73 (1 H, td, J = 11.8, 0.8 Hz), 8.35 (1 H, ddd, J = 15.6, 11.8, 0.9 Hz); ^{13}C NMR (Me_2SO-d_6) δ 165.9, 165.2, 139.5, 138.0, 128.1, 125.5, 62.1, 1.49; MS, m/e (relative intensity) 199 (22.2), 169 (6.2), 97 (12.7), 75 (100), 73 (54.8). Anal. Calcd for $C_{11}H_{18}O_4Si$: C, 54.51; H, 7.49. Found: C, 54.58; H, 7.40. Data for **11b** (obtained from spectra also containing **11a**): partial ^1H NMR (270 MHz, $CDCl_3$) δ 6.00 (1 H, d, J = 11.8 Hz), 6.12 (1 H, d, J = 15.6 Hz), 6.69 (1 H, t, J = 11.8 Hz), 8.52 (1 H, dd, J = 15.6, 11.8 Hz); ^{13}C NMR (Me_2SO-d_6) δ 166.4, 164.5, 140.4, 137.5, 129.8, 123.8, 62.1, 16.8, 1.49.

4-[(*n*-Butoxycarbonyl)methyl]-2-butenolide (12). The acid **14** (200 mg, 1.41 mmol) was stirred in neat thionyl chloride (2 mL) at 55 °C for 1.5 h. The thionyl chloride was removed by vacuum distillation (21 mm) to yield a yellow oil. The oil was dissolved in ether, and at 0 °C *n*-butyl alcohol (324 mg, 4.38 mmol) and pyridine (400 mg, 5.06 mmol) were added. After being stirred at room temperature for 1 h, the reaction was poured into ether (100 mL), washed with aqueous 10% sodium bisulfate (2 × 15 mL) and 10% aqueous potassium carbonate (15 mL), dried ($MgSO_4$), and concentrated in vacuo to yield an orange residue. This residue was purified by chromatography (silica gel plate, 20 × 20 cm) in ethyl acetate–hexane–acetone (45:45:10) to give the ester **12** (107 mg, 38.3%) as a colorless oil: IR (CCl_4) 1792, 1770, 1730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (3 H, t, J = 6.8 Hz), 1.32 (2 H, sextet, J = 6.8 Hz), 1.55 (2 H, pentet, J = 6.8 Hz), 2.58 (1 H, dd, J = 15.5, 7.0 Hz), 2.69 (1 H, dd, J = 15.5, 7.0 Hz), 4.09 (2 H, t, J = 6.8 Hz), 5.36 (1 H, tt, J = 7.0, 1.5 Hz), 6.12 (1 H, dd, J = 5.5 (1.5 Hz), 7.55 (1 H, dd, J = 5.5, 1.5 Hz); MS, m/e (relative intensity) 198 (0.7), 143 (42.8), 142 (45.4), 125 (86.4), 83 (100), 55 (46.3); calcd for $C_{10}H_{14}O_4$ 198.0891, found 198.0891.

Treatment of Lactone 12 with Dabco. To the lactone **12** (16 mg, 0.081 mmol) and Me_2SO-d_6 (0.5 mL) in an NMR tube was added 1,4-diazabicyclo[2.2.2]octane (Dabco) (5 mg, 0.04 mmol). The tube was placed in an oil bath at 65 °C. After 45 min the ^1H NMR spectrum showed no distinguishable protons between δ 4.4 and 8.0 ppm. The lactone **12** was completely consumed.

2-*endo*-(Methoxycarbonyl)-2-*exo*-methyl-5-bicyclo[2.2.1]heptene (17). To the iodo lactone **16**[26] (37.42 g, 0.13 mol) in acetic acid (160 mL) was added zinc dust (34.0 g, 0.52 mol) in four portions, keeping the reaction temperature below 35 °C with an ice bath. After the last addition, the reaction was stirred for 4 h at room temperature. The mixture was then filtered and the precipitate washed with acetic acid (40 mL) and water (100 mL). The combined filtrates were diluted with saturated aqueous sodium chloride (200 mL) and extracted four times with ether (250 mL). The ether was dried ($MgSO_4$) and concentrated in vacuo. Toluene was added and also concentrated in vacuo to remove the last traces of acetic acid. The solid residue was dissolved in methanol (150 mL), and methyl iodide (55.4 g, 0.39 mol) and potassium carbonate (35.9 g, 0.26 mol) were added. The mixture was heated at 50 °C for 12 h, when more methyl iodide (11 g, 0.077 mol) was added. After another 10 h at 50 °C, the mixture was diluted with ether (400 mL) and washed with 10% aqueous potassium carbonate (2 × 80 mL). The ether was dried ($MgSO_4$) and concentrated in vacuo at room temperature. The residue was distilled (bp 112 °C (30 mm), lit. bp[46] 62 °C, (5 mm)) to yield the ester **17** (15.91 g, 73.7%) as a colorless liquid: IR (CCl_4) 3080. 1730; ^1H NMR (CCl_4) δ 1.22–1.60 (6 H, m with s at 1.36), 1.88 1 H, (dd, J = 12.0, 2.5 Hz), 2.61–2.83 (2 H, m), 3.55 (3 H, s), 5.84–6.06 (2 H, m); MS, m/d (relative intensity) 166 (6.4), 101 (16.1), 69 (5.9), 67 (5.9), 66 (100), 41 (7.1); calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0996.

6-*exo*-Hydroxy-2-*endo*-(hydroxymethyl)-2-*exo*-methylbicyclo[2.2.1]heptane (15). To the olefin **17** (7 g, 42.17 mmol) in THF (30 mL) at 0 °C was added borane (28.1 mL of a 1.0 M solution in THF, 28.1 mmol). The reaction was stirred for 1.5 h at room temperature before recooling to 0 °C and addition of aqueous sodium hydroxide (3 N, 60 mL) and 30% aqueous hydrogen peroxide (60 mL). This mixture was stirred at room temperature for 1.5 h, then diluted with ether (1 × 300 mL, 1 ×

(46) Fraser, R. *Can. J. Chem.* **1962**, *40*, 78.

150 mL), washed with 10% aqueous sodium thiosulfate (80 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a 60:40 mixture of hydroxy esters.[47] In a separate flask was placed lithium aluminum hydride (1.9 g, 50.0 mmol) in ether (120 mL). To this was added at 0 °C the above esters in ether (30 mL). The reaction was stirred for 6 h at room temperature, recooled to 0 °C, and carefully quenched with 10% aqueous sulfuric acid (80 mL). The mixture was poured into ethyl acetate (1 × 300 mL, 1 × 150 mL), washed with more 10% aqueous sulfuric acid (50 mL), dried ($MgSO_4$), and concentrated in vacuo to yield an oily solid. The residue was dissolved in hot chloroform, and hexane was added until a slight cloudiness was observed. Upon standing, crystals formed (3.0 g) that were twice again recrystallized from chloroform–hexane to yield the pure diol **15** (1.82 g, 26%): mp 119.5–121 °C; IR ($CHCl_3$) 3605 (sh), 3500–3220 (br), 1210, 1010 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6 with D_2O) δ 0.74 (1 H, dd, J = 12.1, 2.4 Hz), 1.02 (3 H, s), 1.03 (1 H, m), 1.10 (1 H, ddd, J = 12.0, 4.3, 2.9 Hz), 1.33 (1 H, dm, J = 13.1 Hz), 1.40 (1 H, dm, J = 10.0 Hz), 1.55 (1 H, ddd, J = 13.0, 6.5, 2.4 Hz), 1.66 (1 H, dd, J = 10.0, 1.5 Hz), 1.95 (1 H, bs), 3.26 (1 H, d (AB), J = 10.0 Hz), 3.33 (1 H, d (AB), J = 10.0 Hz), 4.17 (1 H, J = 6.5 Hz); MS, m/e (relative intensity) 125 (22.1), 109 (59.7), 108 (31.4), 107 (46.), 105 (33.2), 90 (100), 83 (48.3), 77 (100), 68 (41.2), 67 (79.6), 55 (78.9), 43 (57.1), 41 (47.7). Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.33; M_r 156.1119. Found: C, 69.03; H, 10.29; M_r 156.1116.

6-*endo*-Hydroxy-2-*endo*-(hydroxymethyl)-3-*exo*-methylbicyclo[2.2.1]heptane (21). To a suspension of lithium aluminum hydride (1.58 g, 42 mmol) in ether (70 mL) and THF (10 mL) was added a solution of the lactone **20**[26] (10 g, 66 mmol) in ether (20 mL) at 0 °C. Following the addition the reaction was warmed to room temperature and stirred for 18 h. The reaction was carefully quenched at 0 °C with 10% aqueous sulfuric acid (80 mL) and extracted three times with ethyl acetate (150 mL), and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (50 mL). After being dried ($MgSO_4$), concentrated in vacuo, and placed under high vacuum, the diol **21** (9.9 g, 99%) was obtained as a white solid: mp 204–205 °C (begins to sublime at lower temperature); IR ($CHCl_3$) 3625 (sh), 3550–3100 (br); ^1H NMR ($CDCl_3$) δ 0.88–1.16 (4 H, m with s at 1.04), 1.18–1.70 (4 H, m), 1.88–2.16 (2 H, m), 2.26 (1 H, bs), 3.52 (1 H, d (AB), J = 10 Hz), 3.72 (1 H, d (AB), J = 10 Hz), 4.30 (1 H, ddd, J = 10.0, 5.9, 3.8 Hz), 4.86 (2 H, bs); MS, m/e (relative intensity) 110 (10.8), 109 (20.5), 108 (13.0), 95 (26.7), 94 (100), 81 (76.0), 80 (86.2). Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 68.95; H, 10.41.

2-*endo*-[(Benzoyloxy)methyl]-6-*endo*-hydroxy-2-*exo*-methylbicyclo[2.2.1]heptane (22). To the diol **21** (5.46 g, 35 mmol) and benzoyl chloride (5.11 g, 35 mmol) in ether (50 mL) at −20 °C was added pyridine (4.15 g, 52.5 mmol). The reaction was stirred at −20 °C for 2 h, warmed to room temperature, then diluted with ethyl acetate (2 × 150 mL), washed with 10% aqueous sodium bisulfate (2 × 50 mL) and saturated aqueous sodium bicarbonate (40 mL), dried ($MgSO_4$), and concentated in vacuo to yield a viscous yellow oil. The oil was purified by HPLC (1 column, 8% ethyl acetate–hexane) to yield in order of elution the dibenzoate (0.85 g, 7%), the 2° benzoate (2.0 g, 21.9%), and the desired 1° benzoate **22** (4.33 g, 47%): IR ($CHCl_3$) 3605, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–1.70 (8 H, m with s at 1.15), 1.9–2.42 (4 H, m), 4.22 (1 H, ddd, J = 10.0, 5.0, 3.8 Hz), 4.40 (1 H, d, J = 10.0 Hz), 4.63 (1 H, d, J = 10.0 Hz), 7.20–7.44 (3 H, m), 7.95 (2 H, dd, J = 8.0, 1.0 Hz); MS, m/e (relative intensity) 138 (15.5), 108 (17.2), 105 (100), 94 (35.7), 93 (11.0), 77 (22.5); calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1412.

6-*exo*-(Benzoyloxy)-2-*endo*-[(benzoyloxy)methyl]-2-*exo*-methylbicyclo[2.2.1]heptane (19). Method A (Inversion of Alcohol 22). To triphenylphosphine (1.28 g, 4.89 mmol), benzoic acid (0.517 g, 4.89 mmol), and the alcohol **22** (0.908 g, 3.49 mmol) in benzene (15 mL) at 60 °C was added diethyl azodicarboxylate (0.851 g, 4.89 mmol) in benzene (2 mL). Immediately the orange color of the azo compound disappeared, and the reaction was kept at 60–65 °C for 3 h. Upon cooling to room temperature the mixture was poured into ether (100 mL) and washed with 10% aqueous sodium carbonate (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography (silica gel column, 3 × 15 cm) with 10% ether–hexane to yield a mixture of olefin, inverted ester **19**, and noninverted ester. This mixture was further purified by chromatography (silica gel plate, 20 × 40 cm) in 50% ether–hexane to yield the olefin (60 mg, 7%) and at a lower R_f the mixture of inverted and noninverted esters (294 mg, 27%). The esters were separated by chromatography (silica gel plate, 20 × 40 cm) in two elutions (first with benzene, then with 5% ether–benzene) to yield the less polar noninverted ester and the more polar inverted ester **19** (153 mg, 14%). The inverted ester was recrystallized from hexane (mp 110.5–112 °C).

Method B (Esterification of the Diol 15). The diol **15** (40 mg, 0.256 mmol), benzoyl chloride (93 mg, 0.64 mmol), and pyridine (1 mL) were stirred for 4 h at room temperature. The mixture was diluted with ether (60 mL), washed with 5% aqueous hydrochloric acid (2 × 20 mL), and saturated aqueous sodium bicarbonate (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (silica gel plate, 20 × 20 cm) in 40% ether–hexane to yield the dibenzoate **19** (93 mg, 99%) as a white solid. The solid was recrystallized from hexane (mp 111–112 °C). When samples from methods A and B were combined, no melting point depression was observed (mp 110.5–112 °C): IR ($CHCl_3$) 1730–1710, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.11 (1 H, dd, J = 13.5, 2.8 Hz), 1.15 (3 H, s), 1.37 (1 H, dm, J = 13.5), 1.64–1.81 (3 H, m), 1.85 (1 H, dd, J = 14.8, 3.0 Hz), 2.38 (2 H, bs), 4.09 (1 H, d (AB), J = 10.5 Hz), 4.33 (1 H, d (AB), J = 10.5 Hz), 5.30 (1 H, d, J = 6.0 Hz), 7.32–7.55 (6 H, m), 7.96 (2 H, dd, J = 8.0, 0.7 Hz), 8.0 (2 H, dd, J = 8.0, 0.7 Hz); MS, m/e (relative intensity) 259 (3.2), 137 (3.8), 120 (4.1), 106 (7.5), 105 (100), 84 (12.3), 77 (27.2), 55 (11.9), 43 (13.6), 41 (10.7). Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.82; H, 6.69; M_r 364.1675. Found: C, 75.94; H, 6.55; M_r 364.1672.

2-*endo*-[(*tert*-Butyldimethylsiloxy)methyl]-6-*exo*-hydroxy-2-*exo*-methylbicyclo[2.2.1]heptane (29a). To the diol **15** (600 mg, 3.85 mmol) in DMF were added *tert*-butyldimethylsilyl chloride (576 mg, 3.85 mmol) and imidazole (600 mg, 8.47 mmol). The reagents were stirred at room temperature for 5 h, poured into ether–ethyl acetate (1:1, 100 mL), washed with water (2 × 15 mL) and saturated aqueous sodium bicarbonate (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (silica gel plates, 3 columns, 20 × 40 cm) in 30% ether–hexane to yield the secondary silylated material **29b** (395 mg, 38%) as a colorless oil, which solidified upon standing (mp 61.5–62.5 °C). At a slightly lower R_f was obtained the primary silylated compound **29a** (210 mg, 20.2%) as a colorless oil: IR (CCl_4) 3620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (6 H, s), 0.76 (1 H, bd, J = 12 Hz), 0.93 (9 H, s), 1.02 (3 H, s), 1.2–1.8 (6 H, m), 1.9 (1 H, bs, $W_{1/2}$ = 4 Hz), 2.14 (1 H, bs, $W_{1/2}$ = 9 Hz), 3.33 (2 H, s), 4.12 (1 H, bd, J = 6.0 Hz); MS, m/e (relative intensity) 213 (5.8), 121 (26.0), 82 (26.7), 79 (33.3), 75 (100.0), 73 (30.9), 43 (54.4); calcd for $C_{11}H_{21}O_2Si$ (M − 57) 213.1310, found 213.1299.

(1′*S,2′*R**,4′*R**,6′*R**)-2′-(Hydroxymethyl)-2′-methylbicyclo[2.2.1]heptan-6′-yl 1-Carboxy-2,4-(*E*,*Z*)-butadiene-4-carboxylate (30).** To the alcohol **29a** (374 mg, 1.39 mmol) in THF (6 mL) were added the anhydride **9** (257 mg, 2.07 mmol) and DMAP (252 mg, 2.07 mmol). The mixture was stirred for 18 h at room temperature, diluted with ether (150 mL), washed with 10% aqueous copper sulfate, dried ($MgSO_4$), and concentrated in vacuo to yield 549 mg of a yellow oil. Without purification, the residue was dissolved in DME, and tetra-*n*-butylammonium fluoride (786 mg, 3.0 mmol) was added. The mixture was heated at 72 °C for 13 h and then poured into ether (50 mL) and extracted with cold 10% aqueous potassium carbonate (3 × 30 ml). The base layers were combined, brought to pH 1 with concentrated HCl, and extracted with chloroform (3 × 60 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to yield an oil. The oil was recrystallized from benzene–carbon tetrachloride to yield white crystals. The crystals were further purified by chromatography (Fluorisil, 4 × 15 cm) with 20% ethyl acetate–hexane containing 2% formic acid to yield the hydroxy acid **30** (153 mg, 39.3%) as a white solid. The compound polymerizes upon storage. The yield of this reaction was at times low (11%), in which case a lot of insoluble polymer

(47) The crude ^1H NMR (270 MHz) spectrum showed two peaks for both the methyl group and the methyl ester in a 60:40 ratio.

(48) Schoeller, R.; Treibs, W. *Chem. Ber.* **1961**, *94*, 2978.
(49) Caubere, P. *Top. Curr. Chem.* **1978**, *73*, 72.

was formed: mp 125.5–129 °C dec (CCl_4–benzene); IR ($CHCl_3$) 3620, 3510 (br), 3300–2900 (br), 1710–1695, 1635, 1601, 885 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 0.93–1.89 (6 H, m), 1.11 (3 H, s), 2.11 (1 H, bs), 2.28 (1 H, bs), 2.38 (1 H, d (AB), J = 11.5 Hz), 3.47 (1 H, d (AB), J = 11.5 Hz), 5.17 (1 H, d, J = 6.1 Hz), 5.98 (1 H, d, J = 11.5 Hz), 6.22 (1 H, d, J = 15.9 Hz), 6.82 (1 H, t, J = 11.5 Hz), 8.41 (1 H, ddd, J = 16.0, 11.5, 1.2 Hz); ^{13}C NMR (Me_2SO-d_6) δ 163.6, 161.4, 137.8, 135.3, 127.6, 122.3, 73.2, 66.0, 48.8, 40.4, 40.0, 38.5, 35.8, 34.1, 13.8.

(1′*S,2′*R**,4′*R**,6′*R**)-2′-(Hydroxymethyl)-2′-methylbicyclo[2.2.1]heptan-6′-yl 4-[(Ethylthio)carbonyl]butyl 2,4-(*Z*,*E*)-Muconate (31).** To the acid **30** (62 mg, 0.22 mmol) in acetonitrile (1 mL) were added the iodide **33** (72 mg, 0.265 mmol) and DBU (33.4 mg, 0.22 mmol). The reaction was stirred at room temperature for 2 h, then poured into ether (120 mL), washed with 10% aqueous sodium bisulfate (20 mL) and saturated aqueous sodium chloride (10 mL), dried ($MgSO_4$), and concentrated in vacuo to yield an orange oil. This oil was immediately purified by chromatography (silica gel plate, 20 × 20 cm) in 50% ethyl acetate–hexane to give the thioester **31** (54 mg, 57.9%) as a colorless oil: IR ($CHCl_3$) 3520, 1735–1695 (br), 1640, 1600, 878, 815 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (1 H, d, J = 12 Hz), 1.19 (3 H, s), 1.30 (3 H, t, J = 7.5 Hz), 1.32–1.88 (9 H, m), 2.17 (1 H, bs, $W_{1/2}$ = 4 Hz), 2.37 (1 H, bs, $W_{1/2}$ = 10.5 Hz), 2.61 (2 H, t, J = 7.0 MHz), 2.91 (2 H, t, J = 7.5 Hz), 3.47 (1 H, d (AB), J = 11.2 Hz), 3.58 (1 H, d (AB), J = 11.2 Hz), 4.23 (2 H, t, J = 7.0 Hz), 5.09 (1 H, bd, J = 6.0 Hz), 5.97 (1 H, d, J = 11.5 Hz), 6.13 (1 H, d, J = 15.3 Hz), 6.68 (1 H, t, J = 11.5 Hz), 8.40 (1 H, ddd, J = 15.3, 11.5 1.0 Hz); MS, m/e (relative intensity) 263 (43.2), 225 (25.1), 169 (38.3), 145 (44.2), 125 (70.8), 123 (44.8), 121 (50.8), 108 (100), 101 (84.6), 97 (53.0), 95 (51.5), 93 (55.5), 79 (52.4), 44 (62.9); calcd for $C_{21}H_{32}O_6S$ 424.1920, found 424.1921.

(1*R,3*R**,19*R**,20*S**)-19-Methyl-4,11,17-trioxa-5,10,16-trioxo-6,8-(*Z*,*E*)-tetracyclo[17.2.1.0^{3,20}.0^{6,9}]docosadiene (24) via NBS.** A solution of the hydroxy thioester **31** (10 mg, 0.024 mmol) and *N*-bromosuccinimide (32.5 mg, 0.178 mmol) was stirred in methylene chloride (6 m, 0.004 M in **31**) for 18 h at room temperature in the dark. The mixture was then diluted with methylene chloride (70 mL), washed with 10% aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium chloride (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was purified by chromatography (silica gel plate, 20 × 20 cm) in 33% ethyl acetate–hexane to yield the trilactide **24** (2.8 mg, 32.3%, 78.5% based on recovered starting material) and, at lower R_f, some starting material (5.9 mg, 59%). Analysis of ^1H NMR spectrum of the starting material shows some isomerization to the *E*,*E* diene had occurred.

Via Mercuric Trifluoroacetate. A solution of the thioester **31** (53 mg, contaminated with 25% of the *E*,*E* thioester, 0.094 mmol) and mercuric trifluoroacetate (85.3 mg, 0.25 mmol) in acetonitrile (12.6 mL, 0.01 M in **31**) was stirred for 18 h at room temperature. The reaction was then poured into hexane (100 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was purified by chromatography (silica gel plate, 20 × 20 cm) in 40% ethyl acetate–hexane to yield the trilactide **24** (10 mg, 29%) and an impure sample of thioester **31**, which was mostly the *E*,*E* diene: IR (CCl_4) 1738, 1721, 1640, 1585, 879 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (1 H, dd, J = 12.0, 2.0 Hz), 1.11 (3 H, s), 1.24–2.10 (9 H, m), 2.19 (1 H, s), 2.31 (1 H, bs), 2.49 (2 H, m (ABXY)), 3.90 (1 H, d (AB), J = 11.3 Hz), 4.05 (1 H, d (AB), J = 11.3 Hz), 4.21 (2 H, m (ABXY)), 5.03 (1 H, bd, J = 6.5 Hz), 5.98 (1 H, d, J = 15.5 Hz), 5.99 (1 H, d, J = 10.8 Hz), 6.62 (1 H, td, J = 11.0, 0.8 Hz), 8.27 (1 H, ddd, J = 15.5, 11.0, 1.3 Hz); MS, m/e (relative intensity) 362 (2.3), 142 (33.9), 124 (69.4), 108 (87.4), 101 (100), 93 (33.1), 80 (31.9), 43 (31.0). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; M_r 362.1729. Found: C, 65.95; H, 7.31; M_r 362.1731.

Ethyl 5-Hydroxypentanethioate (32). To ethanethiol (402 mg, 6.49 mmol) in pentane (5 mL) was added *n*-butyllithium (4.32 mL of a 1.5 M solution in hexane, 6.49 mmol) at 0 °C, and the mixture was stirred for 0.5 h at room temperature. The solvent was removed, and methylene chloride (5 mL) was added followed by diethylaluminum chloride (8.77 mL of a 0.74 M solution in toluene). After being stirred for 1 h at room temperature, δ-valerolactone (500 mg, 4.99 mmol) was added as a solution in methylene chloride (3 mL). The reaction was stirred for 1.5 h at room temperature befor being quenched carefully with 10% aqueous sodium bisulfate at 0 °C. The mixture was diluted with ether (150 mL), washed with 10% aqueous sodium bisulfate (2 × 30 mL) and 10% aqueous potassium carbonate (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (Florisil column, 3 × 15 cm) with 10% ethyl acetate–hexane to yield the thioester **32** (678.5 mg, 85%) as a colorless oil: IR (CCl_4) 3550–3350 (br), 1692 cm^{-1}; ^1H NMR (CCl_4) δ 1.19 (3 H, t, J = 7.5 Hz), 1.32–1.92 (4 H, m), 2.48 (2 H, t, J = 7 Hz), 2.78 (2 H, q, J = 7.5 Hz), 2.80 (1 H, s), 3.47 (2 H, t, J = 7.0 Hz); MS, m/e (relative intensity) 145 (1.8), 101 (100), 83 (14.6), 57 (7.6), 55 (21.0); calcd for $C_7H_{14}O_2S$ 162.0715, found 162.0711.

Ethyl 5-Iodopentanethioate (33). To the alcohol **32** (1.3 g, 8.02 mmol) in ether (17 mL) were added triethylamine (1.72 g, 16.78 mmol), *p*-toluenesulfonyl chloride (3.2 g, 16.78 mmol), and DMAP (200 mg). The mixture was stirred at room temperature for 14 h and then refluxed for 12 h. Workup consisted of dilution with ether (200 mL), washing with 10% aqueous sodium bisulfate (2 × 50 mL), drying ($MgSO_4$), and concentrating in vacuo. The resulting oil consisted of the tosylate and tosyl chloride.

Without purification the oil was dissolved in acetone (50 mL), and sodium iodide (5.16 g, 33.9 mmol) was added. The reaction was stirred at room temperature for 18 h in the dark, then poured into ether (200 mL), washed with 10% aqueous sodium thiosulfate (50 mL) and 10% aqueous potassium carbonate (30 mL), dried ($MgSO_4$), and concentrated in vacuo to yield an orange oil. The oil was purified by chromatography (Florisil, 5 × 45 cm) with hexane to give the iodide **33** (1.91 g, 88%) as a pale yellow oil: IR (CCl_4) 1695 cm^{-1}; ^1H NMR (CCl_4) δ 1.24 (3 H, t, J = 7.5 Hz), 1.65–2.10 (4 H, m), 2.56 (2 H, t, J = 7.0 Hz), 2.85 (2 H, q, J = 7.5 Hz), 3.19 (2 H, t, J = 7.0 Hz); MS, m/e (relative intensity) 211 (48.5), 183 (43.1), 145 (40.1), 128 (26.9), 89 (21.7), 73 (26.9), 55 (100); calcd for $C_7H_{13}OIS$ 271.9732, found 271.9730.

(1*S,2*R**,4*R**,6*R**)-2-[[[5-(*tert*-Butyldimethylsiloxy)pentanoyl]oxy]methyl]-5-hydroxy-1-methylbicyclo[2.2.1]heptane (34a).** To the acid **37** (655 mg, 2.82 mmol) and the diol **15** (396 mg, 2.54 mmol) in THF (15 mL) were added DCC (757 mg, 3.67 mmol) and DMAP (61 mg, 0.5 mmol). The reaction was stirred at room temperature for 40 h. The mixture was then diluted with ether, washed with 10% aqueous sodium bisulfate and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated to yield a colorless oil with solid suspended in it. The residue was dissolved in ether and filtered through a plug of Celite to remove the solid. After concentrating in vacuo, the residue was purified by chromatography (silica gel plate, 2 columns, 20 × 40 cm) in 40% ethyl acetate–hexane to yield a 3:1 mixture of the monoesters **34a** and **34b** (536 mg, 64%) as a broad band. Integration of the signals at δ 4.06 (**34a**) vs. 4.93 (**34b**) was used to determine the ratio of products. These were separated by HPLC (1 column, 18% ethyl acetate–hexane) to yield the 2° acylated alcohol **34b** (73 mg, 8.5%), the more polar 1° acylated alcohol **34a** (289 mg, 33.6%), and fractions that were still a mixture (169 mg). **37a**: IR (CCl_4) 3620 (sh), 3500 (br), 1723 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (6 H, s), 0.90 (10 H, s, one proton is under *t*-Bu group), 1.09 (3 H, s), 1.17–1.82 (9 H, m), 1.95 (1 H, s), 2.26 (1 H, bs), 2.37 (2 H, m), 3.62 (2 H, t, J = 6.2 Hz), 3.70 (1 H, d (AB), J = 12.1 Hz), 3.72 (1 H, d (AB), J = 12.1 Hz), 4.06 (1 H, bd, J = 6.1 Hz); MS, m/e (relative intensity) 313 (0.1), 215 (10.3), 175 (100), 101 (16.5), 94 (22.3), 75 (11.7); calcd for $C_{16}H_{29}O_4Si$ (M − 57) 313.1835; found 313.1836.

(1′*S,2′*R**,4′*R**,6′*R**)-2′-[[[(5′-(*tert*-Butyldimethylsiloxy)pentanoyl]oxy]methyl]-2′-methylbicyclo[2.2.1]heptan-6′-yl 1-Carboxy-2-cyclobutene-4-*cis*-carboxylate (Mixture of Diastereomers) (35).** To the alcohol **34a** (117 mg, 0.32 mmol) and the anhydride **9** (59 mg, 0.47 mmol) in THF (2 mL) was added DMAP (57 mg, 0.47 mmol). The reaction was stirred for 18 h at room temperature, then poured into ether (150 mL), washed with 10% aqueous copper sulfate (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to yield the acid **35** (154.8 mg, 98%) as a colorless oil: IR ($CHCl_3$) 3150–2850 (br), 1740–1710 (br), 839 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) [The spectrum of the diastereomeric mixture is very complex so only a partial analysis is given.] δ 0.08 (s), 0.91 (s, silyl *t*-Bu group), 1.09 (s, methyl group), 4.89 (bd, J = 6.1 Hz, CHOC(O)R for one of the two diastereomers), 4.29 (bd, J = 6.1 Hz, CHOC(O)R for one of the two diastereomers), 6.25 (bs, cyclobutene olefin protons).

(1R*,3R*,6R*,9S*,19R*,20S*)- and (1R*,3R*,6S*,9R*,19R*,20S*)-19-Methyl-4,11,17-trioxa-5,10,16-trioxo-7-cis-tetracyclo[17.2.1.0^{3,20}.0^{6,9}]docosene (23). The silyl acid **35** (154 mg, 0.312 mmol) and tetra-*n*-butylammonium fluoride (408 mg, 1.56 mmol) were stirred in THF (2 mL) at room temperature for 3 h. The mixture was then poured into 50% ethyl acetate–ether (180 mL), washed with 10% sodium bisulfate (40 mL) and water (40 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a pale yellow oil. The oil was purified by chromatography (Florisil column, 3 × 25 cm) with 10% ethyl acetate–hexane, 50% ethyl acetate–hexane, and 50% ethyl acetate–hexane (with 2% formic acid). The latter fractions contained the product and were combined and concentrated in vacuo. To the residue was added toluene (10 mL), which was then removed in vacuo. This procedure was repeated twice to remove the last traces of formic acid (note: the water bath never exceeds 55 °C during this process). The resulting oil was placed under high vacuum (0.1 mm) for 18 h to yield the hydroxy acid (118 mg, 100% mass balance).

To the crude hydroxy acid (48 mg, 0.126 mmol) in benzene (25 mL) was added triphenylphosphine (66 mg, 0.252 mmol) and diethyl azodicarboxylate (43.8 mg, 0.262 mmol). The reaction was stirred at room temperature for 36 h and then concentrated in vacuo to yield an orange oil. The oil was purified by chromatography (silica gel plate, 15 × 20 cm) in 50% ethyl acetate–hexane to give the lactone **23** (32.7 mg, 71.6%) as a colorless oil: partial ^{1}H NMR (270 MHz, $CDCl_3$) [The spectrum of the diastereomeric mixture is complex so only a partial analysis is given.] δ 0.91 (d, J = 12 Hz), 1.11 (s, methyl group), 4.75 (bd, J = 6.5 Hz, CHOC(O)R for one of the two diastereomers), 4.80 (bd, J = 6.5 Hz, CHOC(O)R for one of the two diastereomers), 6.18 and 6.28 (both d (AB), J = 3.1 Hz, cyclobutene olefin protons for one of the two diastereomers), 6.25 (bs, cyclobutene olefin protons for one of the two diastereomers).

Thermolysis of Cyclobutene 23. The cyclobutene **23** (35 mg, 0.0966 mmol) in toluene-d_8 (0.55 mL) was heated at 87 °C for 4 h (^{1}H NMR analysis showed no reaction had occurred) and at 106 °C for 41 h. The ^{1}H NMR (270 MHz) spectrum showed a 63:37 mixture of the *E,Z* isomers **24** and **25**, with **24** predominating (integration of the signals at δ 7.80 (**25**) and 8.27 (**24**) was used to determine the isomer ratio). The toluene-d_8 was removed in vacuo and the residue purified by chromatography (silica gel plate, 20 × 20 cm) in 33% ethyl acetate–hexane (three elutions) to yield the *Z,E* isomer **24** (16.2 mg, 46.3%) and at a lower R_f the other *E,Z* isomer **25** (12.1 mg, 34.6%), both as colorless oils. Isomer **24** was identical with the previously prepared *E,Z* macrocycle (vide supra) by ^{1}H NMR (270 MHz), MS, and analytical TLC (25% ethyl acetate–hexane). **25**: IR (CCl_4) 1739, 1718 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (1 d, dd, J = 12.0, 1.9 Hz), 1.18 (3 H, s), 1.1–1.98 (9 H, m), 2.20 (1 H, s), 2.29–2.50 (3 H, m), 3.72 (1 H, d (AB), J = 11.0 Hz), 4.13 (1 H, m), 4.29 (1 H, *d* (AB), J = 11.0 Hz), 4.48 (1 H, m), 4.71 (1 H, bd, J = 6.1 Hz), 5.95 (1 H, d, J = 11.1 Hz), 6.05 (1 H, d, J = 15.5 Hz), 6.68 (1 H, td, J = 11.1, 0.8 Hz), 7.80 (1 H, ddd, J = 15.5, 11.1, 12 Hz); MS, *m/e* (relative intensity) 137 (9.4), 121 (12.7), 108 (39.3), 101 (100), 93 (98.7), 80 (18.5), 55 (40.8), 43 (43.8); calcd for $C_{20}H_{26}O_6$ 362.1729, found 362.1730.

5-(*tert*-Butyldimethylsiloxy)pentanoic Acid (37). To the alcohol **36** (1 g, 8.13 mmol) in methylene chloride (15 mL) were added *tert*-butyldimethylsilyl chloride (1.34 g, 8.94 mmol) and DMAP (1.20 g, 9.83 mmol). The reaction was stirred at room temperature for 19 h, then diluted with ether (200 ml), washed with 10% aqueous sodium bisulfate (2 × 50 mL) and saturated aqueous sodium chloride (40 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was purified by chromatography (silica gel column 3 × 40 cm) with hexane to 25% ether–hexane to yield a silyl ether (1.21 g, 60.5%) as a colorless oil.

To this oil (700 mg, 2.84 mmol) in HMPA (4 mL) was added lithium methyl mercaptide (500 mg, 9.25 mmol). The reaction was stirred at room temperature for 12 h, then poured into 10% chloroform–ethyl acetate (100 mL), and extracted with 10% potassium carbonate (2 × 70 mL). The base extractions were combined, neutralized at 0 °C with solid sodium bisulfate to pH 1, and extracted with ether (3 × 70 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to yield the acid **37** contaminated with 15–20% HMPA. The HMPA was removed under high vacuum (0.1 mm, 14 h) at 40 °C, leaving the acid **37** (524 mg, 78.8%) as a colorless oil: IR ($CHCl_3$) 3400–2900 (br), 1702 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.04 (6 H, s), 0.88 (9 H, s), 1.40–1.80 (4 H, m), 2.35 (2 H, t, J = 7.0 Hz), 3.60 (2 H, t, J = 7.0 Hz), 11.38 (1 H, bs).

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Registry No. **1**, 3148-09-2; **7**, 87729-18-8; **8**, 87729-19-9; **9**, 10374-07-9; (*E,Z*)-**10a**, 87729-20-2; (*E,E*)-**10b**, 87729-21-3; (*Z,E*)-**10b**, 87729-22-4; (*E,Z*)-**11a**, 79568-66-4; (*Z,E*)-**11b**, 87729-23-5; **12**, 87729-24-6; **14**, 6666-46-2; **15**, 22810-52-2; **16**, 13432-80-9; **17**, 7167-29-5; **19**, 87729-25-7; **20**, 38335-10-3; **21**, 87760-80-3; **22**, 87729-26-8; **23** (isomer 1), 87729-27-9; **23** (isomer 2), 87760-81-4; **24**, 87729-28-0; **25**, 87760-82-5; **29a**, 87729-29-1; **29b**, 87729-30-4; **30**, 87729-31-5; **31**, 87729-32-6; **32**, 87729-33-7; **33**, 87729-34-8; **34a**, 87729-35-9; **34b**, 87729-36-0; **35** (isomer 1), 87729-37-1; **35** (isomer 2), 87760-83-6; **36**, 14273-92-8; **36** *tert*-butyldimethylsilyl ether, 87729-38-2; **37**, 87729-39-3; ethanethiol, 75-08-1; δ-valerolactone, 542-28-9.

On the Palladium-Catalyzed Alkylation of Silyl-Substituted Allyl Acetates with Enolates

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Treatment of lithium enolates with trialkylstannyl trifluoroacetates permits their use as nucleophiles in allylic alkylations catalyzed by palladium with high regioselectivity and without polyalkylation. Alkylation without concomitant desilylation occurs for 3-acetoxy-1-(trimethylsilyl)-1-propene and *n*-butyl 2-acetoxy-4-(trimethylsilyl)-3-butenoate under these conditions. The choice of substituents on the tin does affect the rate of the alkylation; trimethyl substitution proceeds substantially faster than tri-*n*-butyl substitution.

Palladium-mediated formation of carbon–carbon bonds in allyl systems begins to emerge as a powerful tool for selective synthetic transformations.[1] In addition to the chemoselectivity, the ability to activate normally inert

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