Total Synthesis of (±)-Dimethyl Jaconate

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The total synthesis of a cyclic necic acid derivative, (±)-dimethyl jaconate, is described as a seven-step sequence starting from 3,4-dichloro-2-furoic acid. The key step involves an intramolecular cycloaddition of furfuryl allyl sulfide **21b**, establishing the desired relative stereochemistry of the three asymmetric centers on the tetrahydrofuran ring. The 1,2-dichloro olefin thus produced is uncovered as a diester equivalent through an ozonolysis reaction in methanol. Raney nickel desulfurization then reduces the linking sulfur bridge to produce the desired target, though as an epimeric mixture at the C6 hydroxyethyl center. This problem is addressed with a study of the stereoselective reductions of intermediate ketones **24** and **25**, with the latter ketone affording a 4:1 ratio of products favoring the desired epimer.

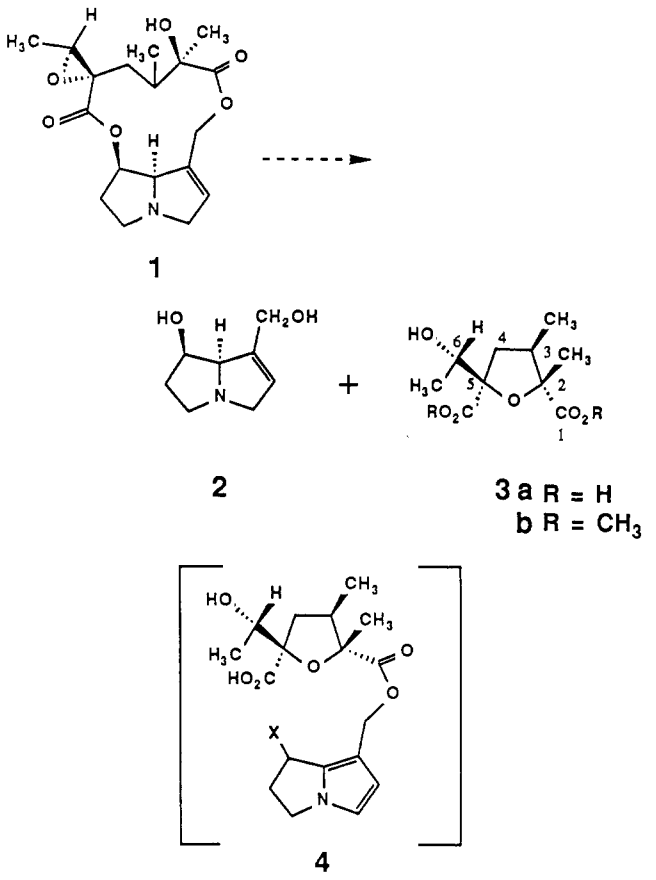
Pyrrolizidine alkaloids such as jacobine **1**, are among the most common alkaloids found in the plant kingdom.[2] Although these compounds are hepatotoxins,[3] several members have shown significant activity against solid tumors such as Adenocarcinoma 755, Sarcoma 180, and several Walker 256 varieties.[4] This activity has also been exhibited by some of the monoester derivatives,[5] which in turn have been found to be intermediates in the metabolism of these alkaloids.[6] The metabolism is presumed to involve partial hydrolysis of the diester chain coupled with an intramolecular cyclization of the α-hydroxyl group where present to afford cyclic monoester **4** (Scheme I, X = H or Nuc). For example, jacobine **1** is readily cleaved under hydrolytic conditions to retronecine **2**, and a cyclic diacid product jaconecic acid **3a** rather than the expected open-chain structure.

In order to evaluate the relationship of antitumor activity to toxicity of various monoester intermediates along this metabolic pathway, we were interested in preparing several of the cyclic diacid portions of these natural products. Jaconecic acid was first isolated by Bradbury and Willis upon basic hydrolysis of jacobine.[7a] The structure of jaconecic acid was solved by Bradbury and Masamune, and the absolute configuration was determined by Masamune in 1960.[7b,c] In 1984 the first synthesis of the cyclic diacid nemorensic acid[8] was reported from our research group, but no synthesis of jaconecic acid has yet appeared. In this report we would like to describe our synthesis of (±)-dimethyl jaconate **3b**, which utilizes dihalofurans as cycloaddition dienes.

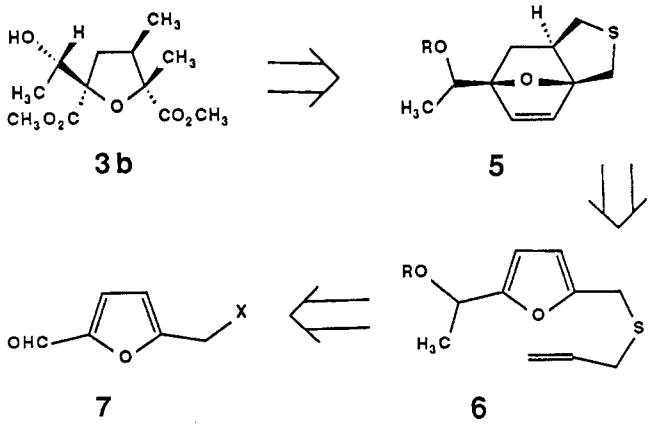
Results and Discussion

Our synthetic approach to this molecule had to account for the formation of the hindered α,α'-substituted tetrahydrofuran. Most approaches to these rings involve the penultimate formation of an oxygen-to-carbon bond. In cases where the α and α' carbons are tri- or tetrasubstituted and when cis relationships of the ring substituents are to be formed as in the case for **3**, this cyclization often works poorly or without stereochemical control.[9] An equally difficult problem involves controlling the stereochemistry of four asymmetric carbons, three of which are contained

Scheme I



Scheme II



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(2) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. *The Pyrrolizidine Alkaloids*; American Elsevier: New York, 1968.

(3) Robins, D. J. *Prog. Chem. Org. Nat. Prod. XCI*; Springer-Verlag: Wein, 1982. Culvenor, C. C. J.; Edgar, J. A.; Jago, M. V.; Outteridge, J. E.; Peterson, J. E.; Smith, L. W. *Chem.-Biol. Interact.* **1976**, *12*, 299.

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(7) (a) Bradbury, R. B.; Willis, J. B. *Aust. J. Chem.* **1956**, 258. (b) Bradbury, R. B.; Masammune, S. *J. Am. Chem. Soc.* **1959**, *81*, 5201. (c) Masamune, S. *J. Am. Chem. Soc.* **1960**, *82*, 5253.

(8) Klein, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 2573.

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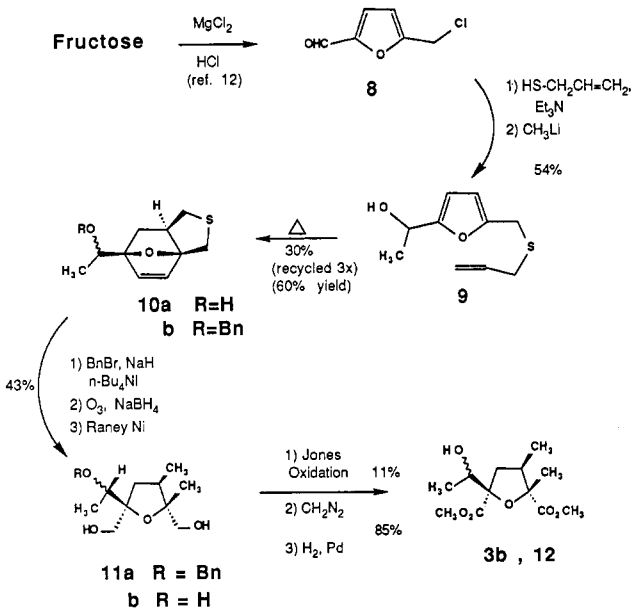
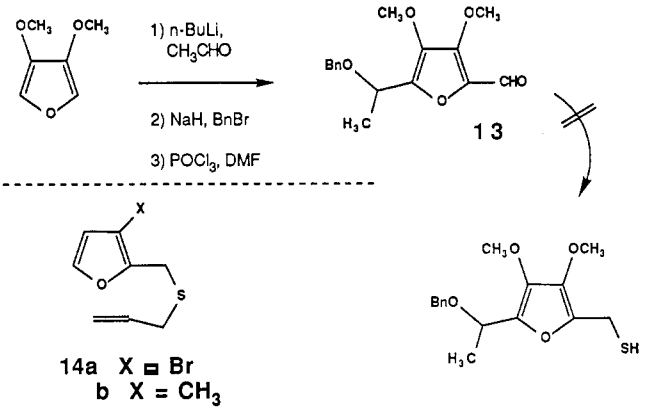
Scheme III



Scheme IV



in the ring nucleus. Applying the chemistry from previous work,[8] we sought to prepare the ring system stereoselectively through an intramolecular cycloaddition reaction of a furfuryl allyl sulfide (Scheme II). Oxidative cleavage and desulfurization of cycloadduct **5** would yield the desired target. Adduct **5** could be derived from the stereoselective cycloaddition of furfuryl allyl sulfide **6**, which in turn could be prepared in a straightforward manner from a simple furan derivative **7**.

The problems associated with the intramolecular cycloaddition of furans has been well documented to date.[10,11] For many simple systems the equilibrium is known to lie on the side of the reactant furan. Methods that have been applied in order to increase the occurrence of conformations leading to proper approach of the diene and dienophile have depended on gross structural effects in the cyclizing system and thus had limited utility. Furthermore, few of these approaches have produced the tetrasubstituted carbon system required for the synthesis of several of the above-mentioned targets. We have successfully applied a concept of structural effects[10] in this general cycloaddition reaction, which produce substantially increased yields of cycloadducts. Placement of a substituent at the C3 position of the furan nucleus develops eclipsing strain with the side chain which is released during the reaction, thus energetically favoring the cycloadduct. It is also well established that intramolecular cycloadditions of dienes such as **6** occur with exclusive exo attack of the dienophile on the diene,[11a] thus establishing the desired stereochemistry of the reacting centers.

Our first approach to jaconecic acid began with 5-(chloromethyl)furfural **8**,[12] accessible from fructose in 81% yield (Scheme III). Treatment of chloride **8** with allylmercaptan, followed by addition of methyllithium afforded alcohol **9**. Cycloaddition of **9** led to an equilibrium mixture of starting material and 35% of adduct **10** as a mixture of diastereomers at the hydroxylated carbon. This low yield was expected from our previous studies, and after recycling three times, a yield of 60% was obtained. Benzylation of **10a**, followed by ozonolytic cleavage of the tricyclic olefin, quenching with sodium borohydride, and subsequent Raney nickel desulfurization gave diol **11a**. This diol was deprotected to **11b** and shown by comparison to literature data[7a] to be a mixture of the authentic triol **11a** and a second component, which was later characterized as its C6 epimer (see below). Thus, control of the stereochemistry of the three-ring centers was established. Jones oxidation of **11a** led to a low yield of diacid, which was further treated with diazomethane and deprotected through hydrogenolysis with palladium to give the dimethyl esters of (±)-jaconecic acid **3b** and its C6 epimer, **12**. The desired ester was isolated via chromatography and was identical with a sample of dimethyl jaconate prepared from jaconecic acid[13] with diazomethane in terms of its ^1H NMR and ^{13}C NMR spectra and GC mass spectroscopy. Unfortunately, numerous attempts to increase the yield of the oxidation step failed.

An approach that would circumvent the two major problems in this synthesis involved incorporating substituents at C3 and C4 of the furan precursor. With alkoxy or halo groups at these positions, the ozonolysis reaction would lead directly to the diester. Furthermore, it is known from previous work that substituents at these positions greatly enhance the cycloaddition yields. We chose to start with 3,4-dimethoxyfuran which was prepared in a multistep sequence from digylcolic acid[14] (Scheme IV). Although aldehyde **13** could be prepared via Vilsmeier methodology, the yield was low and further work failed to produce the desired mercaptan due to instability of the 3,4-dimethoxyfuran system. Alternatively, we studied the utility of chlorofurans as cycloaddition precursors. Little is known about the effect of halides in these reactions, though in one case involving a C3 bromofuran **14a**, the cycloaddition reaction occurs with equal or greater facility than that of the methyl analogue **14b**.[10] Furthermore, examples of ozonolysis of dihalo olefins, though not consistant, have led to the desired diesters in cyclopentene systems.[15] With this in mind we prepared model furan **16** from the known 3,4-dichlorofuroic acid[16] (Scheme V). We were pleased to see that cycloaddition of **16** under

(9) Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825.
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(11) (a) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, 1689. (b) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982**, 303. Pelter, A.; Singaram, B. *Tetrahedron Lett.* **1982**, 245. Williams, D. R.; Phillips, J. C.; Barner, B. A. *J. Am. Chem. Soc.* **1981**, *103*, 7398.
(12) Hamada, K.; Yoshihara, H.; Suzukamo, G. *Chem. Lett.* **1982**, 617.
(13) We wish to thank Dr. C. C. J. Culvenor at the Division of Animal Health, CSIRO, Parkville, Victoria, Australia, for his generous gift of authentic jaconecic acid. A sample of this acid was reacted with excess diazomethane under standard conditions to obtain the dimethyl ester.
(14) Iten, P. X.; Hofmann, A. A.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 430.
(15) Nagendrappa, G.; Griesbaum, K. *J. Agric. Food Chem.* **1978**, *26*, 581.
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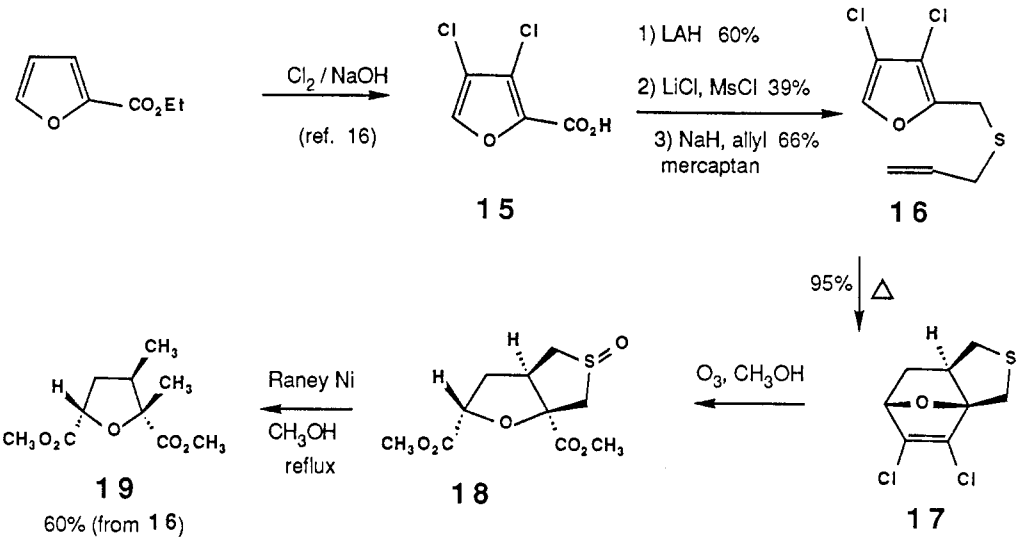
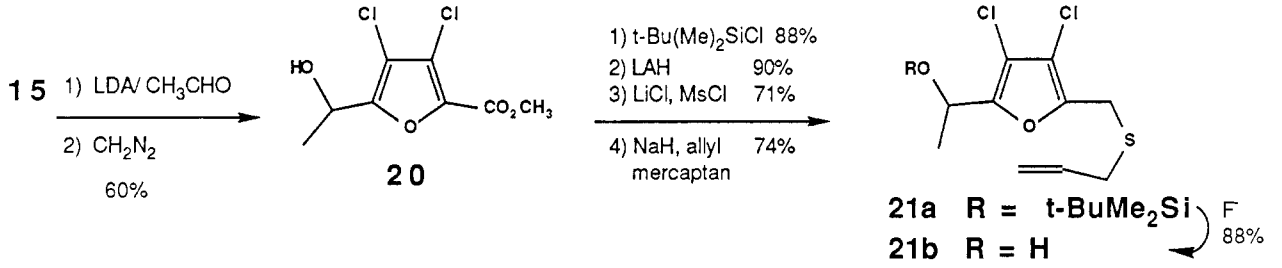
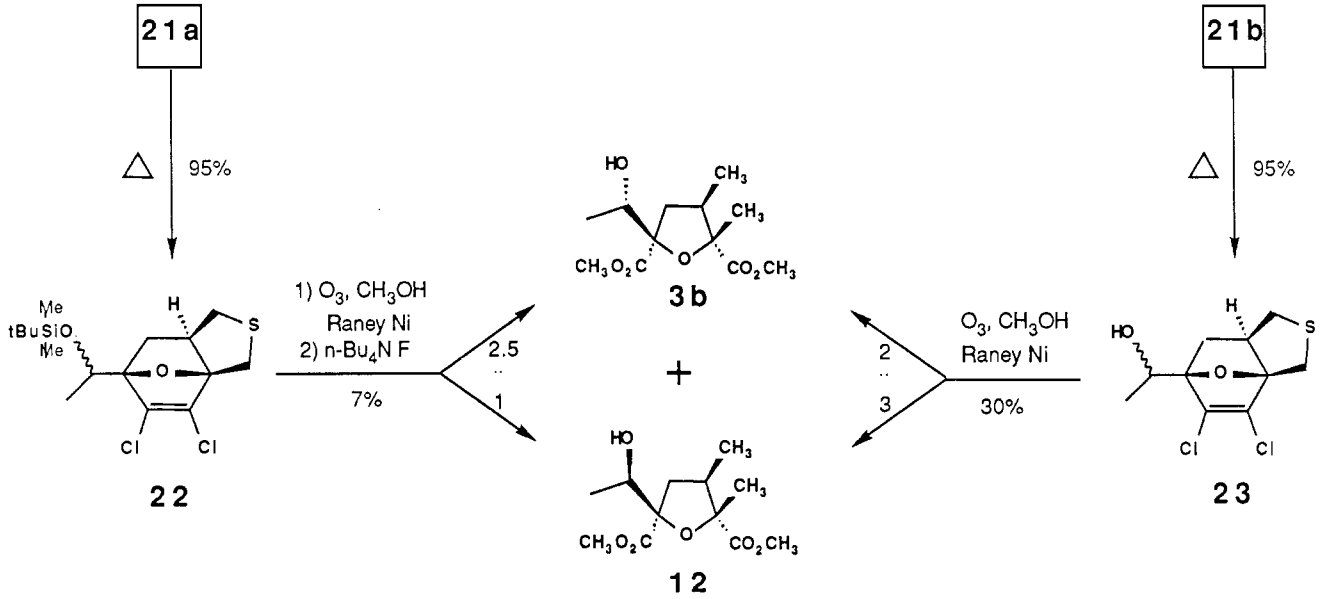
Scheme V



Scheme VI

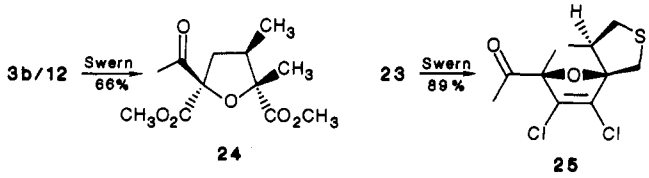




standard conditions gave a 95% yield of adduct **17**. Since the corresponding 3,4-dimethyl adduct is produced in 77% yield at equilibrium, we may be seeing an effect that is related to the electronics of the system. The cycloadduct **17** was treated with ozone in methanol to obtain the dimethyl ester **18**, which was then directly desulfurized with Raney nickel as described above. From previous work it was established that an intermediate sulfoxide is formed and can be isolated from the ozonolysis mixture, but both steps are performed more conveniently in one pot. In this way the model diester **19** was produced in 60% yield. This efficient approach can be used to stereoselectively prepare a wide variety of cyclic diesters.

The synthesis of dimethyl jaconate would involve the inclusion of the hydroxyethyl group on the precursor furan. Treatment of dichloro acid **15** with LDA produces the dianion, which is then quenched with acetaldehyde and diazomethane to afford ester **20** in 60% yield (Scheme VI). Following silylation of the furfurylic hydroxyl group with *tert*-butyldimethylsilyl chloride, the previously described chemistry was applied to give sulfide **21** in 40% total yield. Cycloaddition of **21** under standard conditions leads to adduct **22**, again in 95% yield as a 2.5:1 diastereomeric mixture at the silyloxy center. It is interesting to note that

Table I. Reduction of Ketones 24 and 25



	24 → 3b/12		25 →→ 3b/12	
reducing[a] agent	yield, %	ratio[b] 3b/12	yield, %	ratio[b,c] 3b/12
$NaBH_4$	77	3/5	89	4/1
$Zn(BH_4)_2$	76	1/3	81	3/2
L-Selectride	10	2/3	63	5/1
K-Selectride	61	1/1.8	30	1/2

[a] See the Experimental Section for reaction conditions. [b] Ratios determined by 200-MHz ^1H NMR spectral integration of C6 methine proton. [c] Reduced products carried through to final products.

the unequal production of epimers implies the potential for an enantiomeric synthesis utilizing the influence of the furfurylic hydroxyl group of an optically pure furan analogue. The treatment of **22** with ozone/Raney nickel as in the case of the model system above afforded a low yield (7%) of (±)-dimethyl jaconate (**3b**) and (±)-dimethyl epijaconate (**12**), which were also isolated as a 2.5:1 mixture, respectively.

We found that this oxidation–desulfurization reaction led to a 30% yield of products when the desilylated substrate **23** was used. Alcohol **23** was obtained in 90% yield after initial desilylation of **21a** and subsequent cycloaddition as previously described. Although the yield of **3b** and **12** was higher, the epimeric ratio of 2:3, respectively, was obtained. We therefore investigated the stereoselective reductions of ketones **24** and **25** in order to increase the amount of dimethyl jaconate obtained. Both ketones were prepared via Swern oxidation of the corresponding alcohol epimers **3b/12** and **23** in 66% and 89% yields, respectively. Although a stereoselective bias could not be foreseen in the case of ketone **24**, applying Cram's theories[17] to the tricyclic ketone **25** predicted some discrimination. As seen in Table I we found that reduction of the tricyclic ketone **25** with sodium borohydride gave the best overall results in terms of yield and ratio of epimers. Following this sequence we could then isolate (±)-dimethyl jaconate in 20% yield from cycloadduct **23**. The resultant diester (containing 20% epijaconate) was also refluxed with potassium hydroxide in aqueous ethanol to afford a solid in 66% yield. After recrystallization, diacid **3a** was shown, via spectral comparisons, to be identical with an authentic sample of jaconecic acid.[13]

We have described an example of the effect of halides in the cycloaddition reaction of furans both in enhancing the yields of adducts and in its further application as a diester equivalent. Investigations of the poor yield of the oxidation–desulfurization reaction is in progress, however this short sequence successfully constructs the hindered α,α'-tetrasubstituted tetrahydrofuran ring of jaconecic acid with complete stereocontrol at the three ring carbons.

Experimental Section

The purity of all titled compounds was established to be ≥90% by inspection of ^1H and ^{13}C NMR spectra unless otherwise stated. Melting points are uncorrected.

Preparative thin-layer chromatography (TLC) was performed on plates (thickness 0.50 mm, silica gel 60 F-254) purchased from EM Reagents. Preparative centrifugally accelerated radical TLC was performed with use of plates of 1 and 2 mm thickness prepared with Brinkman silica gel 60 PF 254. Gas–liquid chromatography (GLC) was performed with a flame ionization detector with use of 12-m cross-linked methylsilicone capillary column.

Diethyl ether was distilled from sodium benzophenone and tetrahydrofuran (THF) from potassium benzophenone prior to use. Dichloromethane was distilled from phosphorus pentoxide prior to use. Diisopropylamine and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were distilled from calcium hydride and stored over molecular sieves. *N,N*-Dimethylformamide (DMF) was distilled from barium oxide and stored over molecular sieves. All reactions were run under an atmosphere of nitrogen, which had been passed through a column of anhydrous calcium sulfate.

2-(1-Hydroxyethyl)furfur-5-yl Allyl Sulfide (9). (a) Allylthiolation. Triethylamine (8.8 mL, 60 mmol), sodium iodide (0.63 g, 4.0 mmol), and allylmercaptan (70%, 4.8 mL, 44 mmol) were added to a solution of 5-(chloromethyl)-2-furfural[12] **8** (6.08 g, 40 mmol) in 40 mL of dry THF. This solution was stirred under nitrogen for approximately 10 h, water was added, and the layers were separated. The aqueous layer was extracted twice with dichloromethane, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to give 7.03 g of a brown oil containing 92% (NMR) of the desired product with the remainder mostly 5-methyl-2-furfural. This mixture was used without further purification: ^1H NMR (90 MHz, $CDCl_3$) δ 3.23 (d, J = 6 Hz, 2 H, SCH_2CH), 3.80 (s, 2 H, CH_2S), 4.93–5.30 (m, 2 H, $HC{=}CH_2$), 5.53–6.06 (m, 1 H, $HC{=}CH_2$), 6.40 (d, J = 3 Hz, 1 H, CH, furan), 7.18 (d, J = 3 Hz, 1 H, CH, furan), 9.57 (s, 1 H, HC=O).

(b) Methylation. Crude 5-((allythio)methyl)-2-furfural (7.0 g) was dissolved in 20 mL of dry THF and cooled under nitrogen to −78 °C. Methyllithium (45 mL of a 1.3 M solution in hexane, 58 mmol) was slowly added, and the solution was stirred at −78 °C for 15 min. The reaction was then allowed to warm to room temperature and quenched by the slow addition of saturated ammonium chloride, followed by water. The layers were separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a brown oil. This oil was purified by medium-pressure chromatography (ether–hexane (1:1)) to give 4.39 g (54% from **8**) of **9** as a yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.47 (d, J = 6 Hz, 3 H, CH_3), 3.10 (d, J = 6 Hz, 2 H, CH_2S), 3.13 (broad s, 1 H, OHe, 3.60 (s, 2 H, CH_2), 4.77 (q, J = 6 Hz, 1 H, $HCOH$), 4.93–5.23 (m, 2 H, $HC{=}CH_2$), 5.50–5.93 (m, 1 H, $HC{=}CH_2$), 6.02 (d, J = 3 Hz, 1 H, CH, furan), 6.08 (d, J = 3 Hz, 1 H, CH, furan); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 157.10, 150.57, 133.48, 117.36, 107.84, 105.60, 63.14, 34.02, 26.60, 20.95.

***trans*-7-(1-Hydroxyethyl)-10-oxa-3-thiatricyclo[5.2.1.0^{1,5}]dec-8-ene (10).** Furan **9** (2.14 g, 11.2 mmol) was dissolved in toluene with a few drops of pyridine and heated at reflux for 24 h under nitrogen. The solvent was then removed by high vacuum rotary evaporation, and the crude product was purified by medium-pressure chromatography (hexane–ethyl acetate (1:1)) to give 694 mg of cycloadduct **10a** as a mixture of epimers (1:1) (32%) and 1.18 g of starting material. This starting material was recycled to give 60% cycloadduct after three cycles: ^1H NMR (200 MHz, $CDCl_3$) (2 diastereomers) δ 1.27–1.32 (d × 2, 3 H, CH_3), 1.4–1.84 (m, 2 H, $OCCH_2C$), 2.35 (m, 1 H, SCH_2CH), 2.6 (br s, 1 H, OH), 2.7 (t, 1 H, SCHCH), 3.0–3.15 (d × 2, 1 H, SCH_2CH), 3.2–3.4 (d, 1 H, dd, 1 H, $OCCH_2S$), 4.05–4.3 (q × 2, 1 H, $HOCH$), 6.35–6.5 (m, 2 H, olefin); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 137.10, 137.04, 136.91, 136.02, 99.52, 99.43, 95.26, 94.70, 67.66, 66.47, 51.11, 50.53, 36.64, 35.34, 32.61, 31.90, 18.30, 17.38; HRMS ($C_{10}H_{14}O_2S$) calcd 198.0715, obsd 198.0723.

***trans*-7-(1-(Benzyloxy)ethyl)-10-oxa-3-thiatricyclo[5.2.1.0^{1,5}]dec-8-ene (10b).** Cycloadduct **10a** (694 mg, 3.5 mmol) in 20 mL of dry THF was slowly added to a suspension of sodium hydride (60%, 0.21 g), which had been washed free of oil with hexane under a stream of nitrogen, in 5 mL of dry THF. The mixture was stirred under nitrogen for 0.5 h. Tetrabutyl-

(17) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. Cram, D. J.; Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. The explanations for selectivities in Table I do not directly correlated with any one theoretical model and are still under study.

ammonium iodide (0.04 g) and benzyl bromide (0.5 mL, 4.20 mmol) were added, and the solution was stirred under nitrogen overnight. Water was then added to the resultant suspension, and the layers were separated. The aqueous layer was extracted twice with dichloromethane, and the combined organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude ether was purified with the Chromatotron (2-mm plate, hexane–ethyl acetate (4:1)) to give 718 mg (71%) of benzyl ether **10b**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.29 (d, J = 6 Hz, CH_3), 1.40–1.80 (m, 2 H, CH_2), 2.13–2.50 (m, 1 H, CH), 2.73 (t, J = 9 Hz, HC*H*S), 3.04 (dd, J = 9.75, 6 Hz, 1 H, *H*CHS), 3.33 (s, 2 H, CH_2S), 3.88 (q, J = 6 Hz, 1 H, HCO), 4.67 (s, 2 H, CH_2O), 6.38 (dd, J = 7.5, 3 Hz, 2 H, CH=CH), 7.30 (s, 5 H, aromatic).

Ozonolysis and Raney Nickel Desulfurization of Benzyl Ether 10b. Ozone was bubbled through a solution of **10b** (718 mg, 2.49 mmol) in ethanol at 0 °C until TLC showed no remaining starting material. Sodium borohydride (0.10 g) was slowly added, and the stirred mixture was allowed to warm to room temperature for 2 h. The mixture was then cooled to 0 °C, and acetic acid (50%) was added until no more gas evolved. Brine was added to the solution, and the mixture was extracted three times with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give 574 mg of a glass. This product was used without further purification.

Raney nickel (3 mL of commercial aqueous suspension) was added to an ethanol solution of the crude diol from the ozonolysis of **10b** and the mixture was heated at reflux with stirring under nitrogen for 45 min. The mixture was then filtered through Celite, and the Raney nickel was washed with ethanol. The ethanol was removed by rotary evaporation to give 343 mg (59% from **10b**) of crude diol **11a** as a glass. This diol was used without further purification.

(±)-Dimethyl Jaconate and Epijaconate (3b/12) from 11a. (a) Oxidation of Diol 11a. Chromic acid (1.25 M) was added dropwise to a solution of crude diol **11a** (343 mg) in acetone until an orange color persisted. After the reaction had been stirred for 7 h at room temperature, the acetone was decanted, and the salts were washed four times with acetone. The acetone was removed from these combined organic layers by rotary evaporation, and the residue was dissolved in saturated sodium bicarbonate. The bicarbonate solution was extracted three times with dichloromethane and then acidified with 3 N HCl. After the water had been removed by high-vaccum rotary evaporation, the salts were extracted four times with hot ethyl acetate, and the ethyl acetate was removed by rotary evaporation to give a glass. This glass was dissolved in about 3 mL of methanol and treated with excess diazomethane in ether. After the reaction was allowed to stand overnight, a few drops of acetic acid (50%) were added, and the solution was washed with bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a crude oil. This oil was purified with the Chromatotron (1-mm plate, hexane–ethyl acetate (2:1)) to give the product (85 mg, 11% from **11a**) as a mixture of dimethyl jaconate benzyl ether and its C6 epimer: ^{1}H NMR (200 MHz, $CDCl_3$); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 174.91, 174.67, 173.10, 172.64, 138.67, 138.08, 128.39, 128.15, 127.65, 127.51, 127.37, 90.94, 88.41, 86.50, 86.20, 75.27, 75.10, 73.51, 71.40, 52.44, 52.29, 52.08, 39.94, 39.77, 35.48, 34.42, 19.80, 16.27, 14.07, 13.72; GC–MS, m/z 291.

(b) Hydrogenolysis. A catalytic amount of 5% palladium on carbon was added to a solution of the benzyl ether above in 5 mL of ethanol. The flask was evacuated with a water aspirator three times and purged each time with hydrogen from a baloon. The reaction was stirred for 3 days under hydrogen. The suspension was filtered through Celite to remove the catalyst, and the solvent was removed by rotary evaporation. The flask was evacuated to constant weight to give 86 mg (85%) of a clear oil. This oil was found by GC–MS and HPLC (hexane–ethyl acetate (1:1)) analysis to be a mixture of two compounds. The 200-MHz ^{1}H NMR spectra of this mixture showed two distinct quartets centered at 3.97 and 4.12 ppm in a ratio of 3:2. The minor component of this mixture, whose quartet was centered at 4.12 ppm, was found to have the same ^{13}C NMR, 200-MHz ^{1}H NMR, and GC–MS as authentic dimethyl jaconate obtained from Dr. C. C. J. Culvenor:[13] ^{1}H NMR (200 MHz, $CDCl_3$) (minor isomer) δ 1.01 (d, J = 6.59 Hz, 6 H, CH_3, CH_3CHOH), 1.34 (s, 3 H, CH_3), 1.85 (t, J = 12.37 Hz, 1 H, HC*H*), 2.39 (s, broad, 1 H, O*H*), 2.39–2.65 (m, 2 H, *H*CH, *H*C), 3.75 (s, 3 H, CH_3O), 3.79 (s, 3 H, CH_3O), 4.12 (q, J = 6.56 Hz, 1 H, *H*COH); (major isomer) 1.09 (d, J = 6.74 Hz, 3 H, CH_3), 1.20 (d, J = 6.63 Hz, 3 H, CH_3CHOH), 1.32 (s, 3 H, CH_3), 1.84 (t, J = 12.37 Hz, 1 H, HC*H*), 2.39 (s, broad, 1 H, OH), 2.39–2.65 (m, 2 H, *H*CH, *H*C), 3.78 (s, 6 H, CH_3O), 3.97 (q, J = 6.57 Hz, 1 H, *H*COH); IR (film) 3520, 2980, 2960, 2890, 1740, 1650, 1640, 1380, 1280, 1060; GC–MS, m/z, minor isomer, 217 (2.5), 216 (19.8); major isomer, 217 (2.5), 216 (20.3).

3,4-Dimethoxy-5-(1-(benzyloxy)ethyl)-2-furaldehyde (13). (a) Alkylation. *n*-Butyllithium (1.27 mL, 2.7 M in hexane, 3.4 mmol) was added to a −78 °C solution of 3,4-dimethoxyfuran[14] (400 mg, 3.12 mmol) in 2 mL of dry THF. This mixture was warmed to 0 °C, stirred for 30 min, and then warmed to room temperature and allowed to stir for 1 h. This dar red solution was then cooled to 0 °C, and 0.14 mL of a THF solution containing 147 mg (3.34 mmol) of acetaldehyde was added. This yellow solution was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction was quenched by addition of saturated ammonium chloride. The solution was concentrated by rotary evaporation, and the aqueous layer was saturated with salt and extracted three times with ether. The ether was washed with brine, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give a crude oil. This crude oil was purified with the Chromatotron (2-mm plate, ether–hexane (1:2)) to give 163 mg (30%) of 3,4-dimethoxy-2-(1-hydroxyethyl)furan as a clear oil.

(b) Benzylation. Sodium hydride (104 mg, 50% in mineral oil) was placed in a dry 25-mL flask equipped with a Teflon-coated stir bar and a septum. The flask was flushed with nitrogen, and the sodium hydride was suspended in 1 mL of dry DMF. Alchol from part (a) (220 mg, 1.28 mmol) in 1.5 mL of dry DMF was added, and the mixture was stirred under nitrogen for 0.5 h. Benzyl bromide (0.32) was then added, and the solution was stirred for 2 h at room temperature, before being quenched first with methanol followed by water. The mixture was extracted three times with dichloromethane, and then the organic layer was dried over anhydrous magnesium sulfate and finally concentrated by rotary evaporation to give a yellow oil. This oil was purified with the Chromatotron (2-mm plate, CH_2Cl_2–hexane (1:1)) to give 100 mg (30%) of 2-(1-(benzyloxy)ethyl)-3,4-dimethoxyfuran as a yellow oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.57 (d, J = 7 Hz, 3 H, CH_3CHOBzl), 3.73 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.43 (s, 2 H, CH_2), 4.62 (q, J = 7 Hz, 1 H, *H*COBzl), 6.90 (s, 1 H, CH), 7.30 (s, 5 H, aromatic).

(c) Formylation. Dimethylformamide (1.8 mL) was placed in a dry flask, which has been flushed with dry nitrogen and equipped with a Teflon-coated magnetic stir bar and septum. After the DMF had been cooled to 0 °C, phosphorus oxychloride (0.09 mL) was added, and the mixture was stirred for 10 min. The ether from part (b) (288 mg in 2 mL of DMF) was then added, and the resulting red mixture was stirred at 0 °C for 40 min and then poured into a solution of sodium bicarbonate. The water and DMF were removed by a high|acuum rotary evaporator, and the salts were triturated with dichloromethane. The solution was filtered through a pad of silica gel, and the pad was washed with ethyl acetate. The combined organic solutions were concentrated by rotary evaporation, and the resulting red liquid was purified with the Chromatotron (2-mm plate, ether–hexane (1:1)) to yield 41 mg (13%) of **13** as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.56 (d, J = 6 Hz, 3 H, CH_3CHOBzl), 3.83 (s, 3 H, OCH_3), 4.17 (s, 3 H, OCH_3), 4.50 (s, 2 H, CH_2), 4.63 (q, J = 6 Hz, 1 H, *H*COBzl), 7.33 (s, 5 H, aromatic), 9.57 (s, 1 H, OCH).

2-(3,4-Dichloro)furfuryl Allyl Sulfide (16). (a) Reduction of 15. Lithium aluminum hydride (95%) was suspended in 20 mL of dry THF in a three-necked flask equipped with a reflux condenser. A solution of 1.0 g (5.5 mmol) of 3,4-dichlorofuroic acid[16] (**15**) in THF was slowly added at a rate to maintain reflux. The solution was stirred at room temperature for 2 h and then heated at reflux for 0.5 h. After the reaction was cooled to 0 °C, it was quenched by the slow addition of 0.3 mL of water followed by 0.3 mL of 10% NaOH and 0.9 mL of water. The resulting suspension was stirred at room temperature for 2 h and then filtered through Celite. The precipitate was washed further with

THF, and the combined filtrates were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The oil was distilled bulb-to-bulb (95 °C, 1 mm) to give 560 mg (60%) of 3,4-dichlorofurfurol as a clear oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.63 (broad s, 1 H, OH), 4.57 (s, 2 H, CH_2OH), 7.40 (s, 2 H, furan); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 149.35, 138.35, 116.21, 113.67, 54.50. Anal. Calcd for $C_5H_4Cl_2O_2$: C, 35.96; H, 2.42. Found: C, 35.72; H, 2.42.

(b) Chlorination. 3,4-Dichlorofurfurol (615 mg, 3.68 mmol) was dissolved in 5 mL of DMF containing 233 mg (5.5 mmol) of lithium chloride and 0.97 mL (7.36 mmol) of collidine. This mixture was cooled to 0 °C under nitrogen, and 0.57 mL of methanesulfonyl chloride was added. After the reaction had stirred at 0 °C for 1 h, ice water was added to the semisolid mass, and the resulting solution was extracted twice with hexane. The hexane was washed twice with saturated copper(II) nitrate and once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give the chloride as a yellow oil. This oil was distilled bulb-to-bulb (75 °C, 1 mm) to give 70 mg (39%) of a clear oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.57 (s, 2 H, CH_2Cl), 7.42 (s, 1 H, furan).

(c) Allylthiolation. Sodium hydride (0.15 g, 50%) was washed with dry hexane under a stream of nitrogen and suspended in dry THF. The suspension was cooled to 0 °C, and allylmercaptan (0.22 mL, 70%, 1.94 mmol) was added. The suspension was stirred at 0 °C for 30 min. Furfuryl chloride from part (b) in THF was then slowly added, and the mixture stirred at 0 °C for 20 min. Water was then slowly added, and the mixture was extracted twice with ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a crude oil, which was purified with the Chromatotron (1-mm plate, hexane–dichloromethane (7:1)) to give 200 mg (66%) of **16**, a clear oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.18 (d, J = 6 Hz, 2 H, CH_2SCH_2), 3.67 (s, 2 H, CH_2SCH_2), 4.93–5.27 (m, 2 H, CH_2=CH), 5.47–5.63 (m, 1 H, CH_2=CH), 7.28 (s, 1 H, furan); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 148.42, 137.67, 133.25, 117.90, 116.21, 112.83, 34.73, 24.87.

***trans*-8,9-Dichloro-10-oxa-3-thiatricyclo[5.2.1.0^{1,5}]dec-8-ene (17).** Allyl sulfide **16** (200 mg, 0.90 mmol) was heated as for furan **9**, and the crude oil was purified with the Chromatotron (2-mm plate, hexane–dichloromethane (2:1)) to give 134 mg (95%) of cycloadduct **17** as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.78 (dd, 1 H, OCHC*H* endo) 1.91 (dt, 1 H, OCHC*H* exo), 2.48 (m, 1 H, SCH_2CH), 2.73 (t, 1 H, SC*H*CH), 3.0–3.2 (m, 2 H, OCC*H*SC*H*), 3.45 (d, 1 H, OCC*H*S), 4.9 (d, 1 H, OC*H*); ^{13}C NMR (200 MHz, $CDCl_3$) δ 133.17, 132.02, 102.52, 83.48, 49.89, 36.49, 34.49, 29.48; HRMS ($C_{10}H_{10}Cl_2O_2S$) calcd 263.97786, obsd 263.97789.

Model Diester 19. Ozone was bubbled into a solution of **17** in 15 mL of methanol at 0 °C until no more starting material was seen by TLC. After the reaction was allowed to stand for 10 min, nitrogen was bubbled through the solution to remove excess ozone, and the methanol was removed by rotary evaporation. The crude glass was used in the next step without further purification.

The crude product of ozonolysis was dissolved in approximately 15 mL of ethanol and added to a suspension of Raney nickel (4 mL) in ethanol. The mixture was heated at reflux with stirring for 4 h. The solution was then filtered through Celite, and the Raney nickel was washed with ethanol. The solvent was removed by rotary evaporation, and the crude diester was purified with the Chromatotron (2-mm plate, ether–hexane (1:1)) to give 107 mg (65%) of diester **19** as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (d, J = 6.9 Hz, 3 H, CH_3CH), 1.36 (s, 3 H, CH_3), 1.90–2.10 (m, 1 H, HCH), 2.26–2.40 (m, 1 H, CH_3CH), 2.67 (m, 1 H, HC*H*), 3.75 (s, 3 H, CH_3O), 3.76 (s, 3 H, CH_3O), 4.62 (dd, J = 8.27, 4.56 Hz, *H*COC); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 174.52, 172.65, 86.56, 76.01, 52.23, 52.05, 38.52, 36.71, 19.69, 14.40. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.32; H, 7.79.

Methyl 3,4-Dichloro-5-(1-hydroxyethyl)-2-furoate (20). Tetrahydrofuran (100 mL) was placed in a 250-mL flask and cooled under nitrogen to 0 °C. Diisopropylamine (5.5 mL, 39.2 mmol) was added, followed by the slow addition of *n*-butyllithium (24.5 mL, 1.6 M in hexane, 39.2 mmol). The solution was stirred at 0 °C for 15 min and then cooled to −78 °C. 3,4-Dichlorofuroic acid[16] (3.080 g, 17 mmol) in THF was slowly added to the basic solution, and the mixture was stirred at −78 °C for 30 min. A solution containing 959 mg (21.8 mmol) of freshly distilled acetaldehyde in 3.4 mL of dry THF was slowly added to the dianion of **15**, and the resulting solution was stirred for 10 min at −78 °C. The mixture was then warmed to 0 °C and quenched by slow addition of saturated ammonium chloride followed by water. The solution was made acidic with 3 N HCl, the layers were separated, and the aqueous layer was saturated with sodium chloride and extracted twice with ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude oil was treated with an excess of a solution of diazomethane in ether. After 1 h acetic acid (50%) was added to react with excess diazomethane, and the ether solution was washed with bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude brown oil was purified by MPLC (ether–hexane (1:1)) to give 2.42 g (60%) of **20**, a light yellow oil (bp 145–155 °C, 1 mm, bulb-to-bulb): ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.58 (d, J = 6 Hz, 3 H, CH_3), 3.07 (broad s, 1 H, OH), 3.92 (s, 3 H, CH_3OH), 5.05 (broad q, J = 6 Hz, 1 H, *H*COH); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 157.72, 154.80, 137.63, 123.83, 113.91, 62.11, 52.21, 20.64; HRMS ($C_8H_8Cl_2O_4$) calcd 237.97936, obsd 237.97990.

3,4-Dichloro-5-(1-(*tert*-butyldimethylsiloxy)ethyl)-furfur-2-yl Allyl Sulfide (21a). (a) Silylation. Hydroxy ester **20** (1.573 g, 6.6 mmol) was dissolved in 3 mL of dry DMF. Imidazole (1.34 g, 19.7 mmol, 3 equiv) and *tert*-butyldimethylchlorosilane (1.50 g, 9.8 mmol, 1.5 equiv) were added, and the solution was stirred under nitrogen at 60 °C for 10 h. Sodium bicarbonate and then water were added, and the solution was extracted three times with a 1:1 mixture of ether–hexane. The organic layer was then washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a yellow oil. This oil was purified by MPLC (ether–hexane (1:1)) to give 2.028 g (88%) of silyl ether as a clear oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.03 (s, 3 H, CH_3SiCH_3), 0.08 (s, 3 H, CH_3SiCH_3), 0.87 (s, 9 H, *tert*-butyl), 1.57 (d, J = 6 Hz, 3 H, CH_3CH), 3.90 (s, 3 H, CH_3O), 4.98 (q, J = 6 Hz, 1 H, *H*COH); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 157.46, 155.20, 137.42, 123.56, 113.18, 62.75, 51.90, 25.51, 21.78, 17.91, −5.12, −5.09.

(b) Reduction. Silyl ether from part (a) (4.02 g, 11.2 mmol) was dissolved in 150 mL of dry dichloromethane and cooled under nitrogen to −78 °C. Diisobutylaluminum hydride (28 mL, 1 M in hexane, 28 mmol) was slowly added via syringe, and the resulting mixture was stirred for 0.5 h. The mixture was then warmed to 0 °C, and the reaction was quenched by the slow addition of 2 mL of methanol followed by 3.8 mL of water. The mixture was stirred for 1 h in the open. Water was added dropwise to form a granular precipitate. The suspension was filtered through Celite, and the precipitation was washed with excess dichloromethane. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give 3.25 g (90%) of the furfuryl alcohol as a clear oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ −0.03 (s, 3 H, $CHSiCH_3$), 0.07 (s, 3 H, CH_3SiCH_3), 0.87 (s, 9 H, *tert*-butyl), 1.45 (d, J = 6 Hz, 3 H, CH_3CH), 2.72 (broad s, 1 H, OH), 4.57 (broad s, 2 H, CH_2OH), 4.93 (q, J = 6 Hz, 1 H, HCOSi); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 151.44, 147.69, 113.63, 111.01, 62.26, 54.67, 25.63, 20.00, 18.01, −5.08, −5.19. Anal. Calcd for $C_{13}H_{22}Cl_2O_3Si$: C, 48.00; H, 6.77. Found: C, 47.77; H, 6.77.

(c) Chlorination. Alcohol from part (b) (3.249 g, 10 mmol) was treated as for 3,4-dichlorofurfurol to give a yellow oil. The crude product was purified by MPLC (hexane–ether (3:1)) to give 2.440 g (71%) of the corresponding chloride as a clear oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.07 (s, 3 H, CH_3SiCH_3), 0.17 (s, 3 H, CH_3SiCH_3), 0.98 (s, 9 H, *tert*-butyl), 1.58 (d, J = 6 Hz, 3 H, CH_3CH), 4.63 (s, 3 H, CH_2Cl), 5.00 (q, J = 6 Hz, 1 H, HCOSi); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 152.61, 144.21, 115.30, 111.31, 62.42, 34.64, 25.71, 22.13, 18.21, −5.02. Anal. Calcd for $C_{13}H_{21}Cl_3O_2Si$: C, 45.42; H, 6.16; Cl, 30.94. Found: C, 45.48; H, 6.31; Cl, 31.04.

(d) Allylthiolation. The chloride from part (c) 1.937 g (5.66 mmol) was treated as in the preparation of **16** and was purified by MPLC (hexane) to give **21a** as a clear oil (1.748 g, 74%): ^{1}H NMR (90 MHz, $CDCl_3$) δ −0.013 (s, 3 H, CH_3SiCH_3), 0.06 (s, 3 H, CH_3SiCH_3), 0.89 (s, 9 H, *tert*-butyl), 1.43 (d, J = 6 Hz, 3 H, CH_3CH), 3.12 (d, J = 7 Hz, 2 H, CH_2SCH_2), 3.58 (s, 2 H, CH_2SCH_2), 4.88 (q, J = 6 Hz, 1 H, HCOSi), 5.00–5.30 (m, 2 H,

CH_2=CH), 5.50–5.97 (m, 1 H, CH_2=C*H*); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 150.86, 146.65, 133.28, 117.77, 112.36, 110.81, 62.16, 34.64, 25.73, 24.70, 22.19, −4.93, −5.06.

***trans*-7-(1-(*tert*-Butyldimethylsiloxy)ethyl)-8,9-dichloro-10-oxa-3-thiatricyclo[5.2.1.0^{1,5}]dec-8-ene (22).** Allyl sulfide **21a** (380 mg, 1 mmol) was heated as for furan **9**, and the crude product was purified with the Chromatotron (2-mm plate, hexane–dichloromethane (4:1)) to give 352 mg (93%) of cycloadduct **22**, a clear oil, as a 2:1 mixture of two diastereomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.35 (s, 6 H, CH_3Si), 0.92 (s, 9 H, *tert*-butyl), 1.33 (d, *J* = 5.96 Hz, 3 H, CH_3, major isomer), 1.37 (d, *J* = 5.96 Hz, 3 H, CH_3, minor isomer), 1.49–2.06 (m, 2 H, CH_2), 2.37–2.56 (m, 1 H, CH), 2.73 (t, *J* = 11.97 Hz, 1 H, *H*HCS), 2.74 (t, *J* = 11.97 Hz, 1 H, *H*HCS), 2.98–3.18 (m, 2 H, SCH_2), 3.42 (d, *J* = 10.43 Hz, 1 H, H*H*CS), 4.08 (q, *J* = 5.96 Hz, 1 H, *H*COH, minor isomer), 4.2 (q, *J* = 5.96 Hz, 1 H, *H*COH, major isomer); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 133.86, 133.82, 133.30, 133.03, 101.06, 100.85, 96.05, 95.06, 68.82, 66.38, 52.46, 52.07, 37.46, 36.71, 36.61, 34.84, 29.70, 29.51, 25.88, 25.74, 19.55, 19.18, 18.17, 18.01, −4.09, −4.14, −4.82. Anal. Calcd for $C_{16}H_{26}Cl_2O_2SSi$: C, 50.38; H, 6.87. Found: C, 50.32; H, 6.87.

(±)-Dimethyl Jaconate and Epijaconate (3b/12) from 22. Ozone was bubbled into a solution of 352 mg (0.92 mmol) of **22** in methanol at 0 °C until no more starting material was detected by TLC. Nitrogen was then bubbled through the solution to remove excess ozone, and the methanol was removed by rotary evaporation to give a glass. This glass was used in the next step without further purification.

The crude product of ozonolysis was dissolved in ethanol (15 mL) and added to a suspension of Raney nickel (3 mL) in ethanol. This mixture was heated at reflux under nitrogen with stirring for 3 h. The solution was then filtered through Celite, and the Raney nickel was washed with ethanol. The solvent was removed by rotary evaporation, and the crude was glass dissolved in ether, filtered through Celite, and concentrated to give 76 mg of crude oil. Analysis of this crude oil by GC–MS showed partial loss of the protecting group.

The product was treated with 1 mL of tetrabutylammonium fluoride (1 M in THF) for 15 min. Bicarbonate was then added, the layers were separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give an oil. This oil was purified with the Chromatotron (1-mm plate, ether) to give 17 mg (7%) of a clear oil. This oil was found by ^{1}H NMR and GC–MS to consist of a 2.5:1 mixture of dimethyl jaconate **3b** and its epimer **12**.

3,4-Dichloro-5-(1-hydroxyethyl)furfur-2-yl Allyl Sulfide (21b). Silyl ether **21a** (731 mg, 1.91 mmol) was cooled to 0 °C and 5 mL of a 1 M solution of tetrabutylammonium fluoride in THF was slowly added. The resulting mixture was stirred at 0 °C for 30 min. Bicarbonate was then added to the solution, and the mixture was extracted three times with ether. The ether was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a crude oil. This oil was purified with the Chromatotron (2-mm plate, ether–hexane (1:1)) to give 483 mg (95%) of **21b**, a clear oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.57 (s, d, *J* = 6 Hz, 3 H, CH_3CH), 2.40 (broad s, 1 H, OH), 3.14 (d, *J* = 6.3 Hz, 2 H, CH_2SCH_2), 3.63 (s, 2 H, CH_2SCH_2), 4.87 (broad q, *J* = 6 Hz, 1 H, *H*COH), 5.07–5.37 (m, 2 H, HC=CH_2), 5.53–6.07 (m, 1 H, *H*C=CH_2).

***trans*-8,9-Dichloro-7-(1-hydroxyethyl)-10-oxa-3-thiatricyclo[5.2.1.0^{1,5}]dec-8-ene (23).** Allyl sulfide **21b** (240 mg, 0.9 mmol) was heated as for furan **9**, and the crude product was purified with the Chromatotron (2-mm plate, ether–hexane (1:1)) to give 229 mg (95%) of **23**, a light yellow oil, as a mixture of diastereomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.77 Hz, 3 H, CH_3e, 1.67–1.80 (m, 1 H, *H*CH), 2.03 (dd, J_1 = 14.61 Hz, J_2 = 2.53 Hz, 1 H, HC*H*), 2.07 (broad s, 1 H, OH), 2.40–2.60 (m, 1 H, HC), 2.78 (t, *J* = 10.61 Hz, 1 H, *H*HCS, minor isomer), 2.80 (t, *J* = 10.61 Hz, 1 H, *H*HCS, major isomer), 3.18 (dd, J_1 = 11.89 Hz, J_2 = 11.22 Hz, 1 H, H*H*CS), 3.16 (d, *J* = 13.03 Hz, 1 H, SC*H*H), 3.50 (d, *J* = 13.16 Hz, 1 H, SCH*H*), 4.21 (q, *J* = 6.75 Hz, 1 H, *H*COH, major isomer), 4.27 (q, *J* = 6.75 Hz, 1 H, *H*COH, minor isomer); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 133.32, 133.19, 101.13, 101.03, 95.48, 66.28, 65.60, 52.13, 36.45, 36.33, 35.01, 34.74, 29.44, 18.41, 17.39; HRMS ($C_{10}H_{12}Cl_2O_2S$) calcd 265.99343, obsd 265.99423.

(±)-Dimethyl Jaconate and Epijaconate (3b/12) from 23. Ozone was bubbled into a solution of 462 mg (1.73 mmol) of **23** in methanol at 0 °C until no starting material was seen by TLC. Dry nitrogen was then bubbled through the solution to remove excess ozone, and the methanol was removed by rotary evaporation. This glass was dissolved in ethanol and added to a suspension of 4 mL of Raney nickel. The mixture was heated at reflux under nitrogen with stirring for 14 h. The solution was then filtered through Celite, the Raney nickel washed with ethanol, and the ethanol was removed by rotary evaporation to give a glass. This glass was dissolved in ether, filtered through Celite, concentrated by rotary evaporation, and the crude product was purified with the Chromatotron (2-mm plate, ether) to give 133 mg (30%) of a clear oil. This oil was found by GC–MS to be a mixture (ca. 1:1) of dimethyl jaconate **3b** and its epimer **12**.

Dimethyl Jaconate Ketone (24). Oxalyl chloride (0.1 mL, 1.2 mmol) was added to 3 mL of dry dichloromethane under nitrogen at −78 °C. Dimethyl sulfoxide (0.18 mL, 2.4 mmol) was then added, and the mixture was stirred for 5 min. A mixture of dimethyl jaconate and its epimer **3b/12** (67 mg, 0.26 mmol in 2 mL of dichloromethane) was then slowly added, and the mixture was stirred at −78 °C over a period of 20 min. Triethylamine (0.84 mL, 6 mmol) was then added; the solution was stirred at −78 °C for 5 min and allowed to come to room temperature. The mixture was poured over ice water, the layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give an orange oil. This oil was purified with the Chromatotron (1-mm plate, ether) to give 44 mg (66%) of a light yellow oil whose spectra were identical with those reported for dimethyl jaconate ketone:[18] ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.46 Hz, 3 H, CH_3), 1.40, (s, 3 H, CH_3), 1.87–2.05 (m, 1 H, *H*CCH_3), 2.33 (s, 3 H, CH_3C=O), 2.52–2.82 (m, 2 H, CH_2), 3.73 (s, 3 H, CH_3O), 4.18 (s, 3 H, CH_3); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 205.30, 173.85, 169.56, 91.17, 88.17, 52.90, 39.73, 38.95, 25.25, 19.45, 14.26; IR (film) 2980, 1750, 1450, 1390, 1370, 1215, 1210 cm^{-1}.

Tricyclic Ketone 25. Cycloadduct **23** (452 mg, 1.69 mmol) in 5 mL of dry dichloromethane was oxidized as for the **3b/12** mixture. The crude product was purified with the Chromatotron (2-mm plate, ether–hexane (1:1)) to give 399 mg (89%) of **25** as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.96 (m, 2 H, OCHCH_2), 2.32 (s, 3 H, CH_3), 2.55 (m, 1 H, SCH_2CH), 2.68 (t, 1 H, SC*H*CH), 3.1–3.25 (m, 2 H, OCC*H*SC*H*), 3.5 (d, 1 H, OCC*H*S); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 202.10, 133.74, 132.27, 102.00, 94.53, 51.64, 36.35, 36.05, 29.43, 26.88; HRMS ($C_{10}H_{10}Cl_2O_2S$) calcd 263.9776, obsd 263.9779.

Sodium Borohydride Reduction of Ketone 24. Ketone **24** (27 mg, 0.1 mmol) was dissolved in 3 mL of ethanol and cooled to 0 °C. Sodium borohydride (10 mg) was added, and the solution was stirred at 0 °C for 1 h. Water (1 mL) was added, and the solution was made acidic by the addition of 1 N HCl. The mixture was then extracted three times with ether, and the ether was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give 20 mg (77%) of a mixture (3:5, 200-MHz ^{1}H NMR) of dimethyl jaconate **3b** and epidimethyl jaconate **12**.

Zinc Borohydride Reduction of Ketone 24. A solution of zinc borohydride (0.21 M) was prepared by adding a solution of freshly fused zinc chloride (982 mg) in ethyl ether (10 mL) to a suspension of 217 mg of 98% sodium borohydride in 20 mL of ethyl ether, and the solution was stirred overnight under nitrogen. The zinc borohydride (2 mL, ca. 0.42 mmol) was added to a −78 °C ethyl ether solution (2 mL) of **24** (44 mg, 0.17 mmol), and the solution was stirred at −78 °C under nitrogen for 1 h. The mixture was then warmed to 0 °C and quenched by the slow addition of water. Acetic acid (50%) was added dropwise to dissolve the solid material, and the solution was extracted three times with ether. The ether was washed with bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary

(18) Yamada, K.; Tatematso, H.; Hirata, Y.; Haga, M.; Hirono, I. *Chem. Lett.* **1976**, 1123.

evaporation to give 33.9 mg (76%) of a mixture (1:3, 200-MHz ^{1}H NMR) of dimethyl jaconate and its epimer.

L-Selectride Reduction of Ketone 24. Ketone **24** (30 mg, 0.12 mmol) was dissolved in 2 mL of dry THF and cooled under nitrogen to −78 °C. L-Selectride (nAldrich; 0.2 mL, 1 M in THF, 0.2 mmol) was slowly added via syringe, and the mixture was stirred under nitrogen at −78 °C for 0.5 h. The reaction was then quenched by the slow addition of 2 mL of saturated ammonium chloride and water. The resulting mixture was extracted three times with ether, and then the ether was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a crude oil. This material was purified with the Chromatotron (1-mm plate, ether) to give 3 mg (10%) of a mixture (1:1.5, 200-MHz ^{1}H NMR) of dimethyl jaconate and its epimer.

K-Selectride Reduction of Ketone 24. Ketone **24** was dissolved in 3 mL of dry THF and cooled under nitrogen to −78 °C. K-Selectride (Aldrich; 0.44 mL, 1 M in THF, 0.44 mmol) was added via syringe, and the solution was stirred at −78 °C for 1 h. The reaction was then warmed to 0 °C and quenched by the addition of 0.33 mL of 1.6 M NaOH followed by the slow addition of 0.14 mL of 30% hydrogen peroxide. The mixture was allowed to warm to room temperature, made acidic with 3 N HCl, and extracted three times with ether. The ether was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a yellow oil. This oil was purified with the Chromatotron (1-mm plate, ether) to give 35 mg (61%) of a mixture (1:1.8, 200-MHz ^{1}H NMR) of dimethyl jaconate and its epimer.

Sodium Borohydride Reduction of Ketone 25. Ketone **25** (321 mg, 1.22 mmol) was reduced as described for ketone **24** to give 287 mg (89%) of a clear oil. The ozonolysis and Raney Nickel desulfurization of this material gave a mixture (4:1, 200-MHz ^{1}H NMR, GC–MS) of dimethyl jaconate and its epimer: ^{13}C NMR of major isomer (50.31 MHz, $CDCl_3$) δ 174.42, 172.73, 90.31, 86.45, 67.80, 52.50, 39.92, 34.01, 19.97, 16.97, 14.14.

L-Selectride Reduction of Ketone 25. Ketone **25** was reduced with L-Selectride (0.62 mL, 1 M in THF, 0.62 mmol) as for ketone **24**. The crude oil was purified with the Chromatotron (1-mm plate, ether–hexane (1:1)) to give 80 mg (63%) of a solid (mp 85–90 °C). The ozonolysis and Raney nickel desulfurization of this material gave a mixture (5:1, 200-MHz ^{1}H NMR, GC–MS) of dimethyl jaconate and its epimer.

Zinc Borohydride Reduction of Ketone 25. An ether solution of zinc borohydride (8 mL, 0.18 M, 1.44 mmol) was used to reduce ketone **25** (199 mg, 0.75 mmol) as for ketone **24** to give 162 mg (81%) of a solid (mp 83–90 °C). The ozonolysis and Raney nickel desulfurization or this material gave a mixture (1.5:1, 200-MHz ^{1}H NMR, GC–MS) of dimethyl jaconate and its epimer.

K-Selectride Reduction of Ketone 25. Ketone **25** (199 mg, 0.75 mmol) was reduced described as for ketone **24**. The crude oil was purified with the Chromatotron (1-mm plate, ether–hexane (1:1)) to give 57 mg (30%) of a 1:2 mixture (200-MHz ^{1}H NMR) of the tricyclic alcohols leading to dimethyl jaconate and its epimer. A second less polar component (44 mg) was isolated and found to be the product of reduction of the double bond.

Jaconecic Acid (3a). A 5:1 mixture of synthetic dimethyl jaconate and its epimer (22 mg), from the L-Selectride reduction of **25** was dissolved in about 4 mL of 80% ethanol containing 0.4 g of KOH. This solution was heated at reflux for 2 h, the ethanol was removed, and the slurry was dissolved in water. This aqueous solution was extracted with ether and made acidic with 3 N HCl. The water was removed by high-vacuum rotary evaporation. The salts were extracted with hot ethyl acetate three times, and the solvent was removed by rotary evaporation to give 13.4 mg (66%) of a light yellow solid. Recrystallization gave pure (±)-jaconecic acid (mp 170–175 °C, ethyl acetate/hexane): ^{1}H NMR (200 MHz, acetone-d_6) δ 1.07 (d, J = 6.42 Hz, 3 H, CH_3CH), 1.24 (d, J = 6.44 Hz, 3 H, CH_3CH(OH)), 1.32 (s, 3 H, CH_3), 1.70–1.80 (m, 1 H, CH), 2.25–2.50 (m, 2 H, CH_2), 4.05 (q, J = 6.44 Hz, 1 H, HCOH). The 200-MHz ^{1}H NMR spectrum is identical with that of an authentic sample of jaconecic acid.[13]

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Syntheses of (−)-2,8a- and (−)-8,8a-Di-*epi*-swainsonine and Evaluation of Their Inhibitory Activity against Several Glycosidases[1]

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Two stereoisomers of the potent α-D-mannosidase inhibitor, swainsonine (**1**), namely, (−)-2,8a- (**5**) and (−)-8,8a-di-*epi*-swainsonine (**6**), have been synthesized from the known azido alcohol **7**. The synthesis of **5** was accomplished via a configurational inversion at C-2 of (1*S*,2*R*,8*R*,8a*S*)-1,8-bis(benzyloxy)-2-[(methylsulfonyl)-oxy]octahydro-5-indolizinone (**10**), which in turn was prepared from the previously reported disubstituted 2-piperidone **8**. The synthesis of **6** involved (1) 2-piperidone (δ-lactam) formation from both of the geometrical isomers of ethyl (4*R*,5*S*,6*S*,7*R*)-5-azido-4-(benzyloxy)-8-[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedi-oxy)-2-octenoate (**19**-*E* and **19**-*Z*) by reduction of the azido group and the double bond followed by desilylation accompanied with cyclization for construction of the 2-piperidone skeleton and (2) stereochemical inversion at C-8 of (1*S*,2*R*,8*R*,8a*R*)-1,2-(isopropylidenedioxy)-8-[(methylsulfonyl)oxy]octahydro-5-indolizinone (**23**). Preliminary bioassays of (−)-2,8a- (**5**) and (−)-8,8a-di-*epi*-swainsonine (**6**) for the glycosidase inhibitory activity reveal that **6** is a potent inhibitor of human lysosomal α-D-mannosidase.

(−)-Swainsonine (**1**), (1*S*,2*R*,8*R*,8a*R*)-octahydro-1,2,8-indolizinetriol, was first isolated from the fungus *Rhizoctonia leguminicola* by Broquist et al. in 1973.[2] This novel indolizidine alkaloid 1 has also been isolated from several

(1) The present work was presented at the 54th National Meeting of the Japan Chemical Society in Tokyo, April 1–4, 1987.

(2) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055.

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