colorless crystals, mp 85.9–86.8 °C (from hexane). Analytical data (IR, ^{1}H NMR, MS, and GC retention time) were identical with those of natural 4. HRMS calcd for $C_{13}H_{20}O_2$ M^+ m/z 208.1462, found M^+ m/z 208.1474.

Dehydration of 3,4-Didehydro-β-ionol (5). A mixture of 5 (300 mg, 1.56 mmol) and 5% aqueous citric acid (60 mL) was refluxed for 1 h. After the usual workup of the mixture, the residue was chromatographed on silica gel (hexane) to give 217 mg (80%) of 1 as a colorless oil.

X-ray Structure Determination of 13. Slow evaporation of a petroleum ether solution afforded colorless crystals suitable for single-crystal X-ray diffraction. A specimen, approximately 0.47 × 0.34 × 0.32 mm, was used. Preliminary photographic data indicated the triclinic space group $P1$ or $P\bar{1}$; a successful structure determination was accomplished in $P\bar{1}$. **Unit cell parameters:** a = 11.112 (2) Å, b = 11.355 (3) Å, c = 7.982 (2) Å, α = 105.36 (2)°, β = 89.78 (2)°, γ = 113.28 (2)°, V = 886.3 (3) Å^3, Z = 2, D_x = 1.2922 (4) g cm^{-3}.

Intensities for the independent reflections for $2\theta < 50°$ were measured with the ω–2θ continuous scan mode at a 2θ rate of 4° min^{-1} by use of graphite-monochromated Mo K_α radiation (λ = 0.71069 Å). The scan width in 2θ was (2.0 + 0.68 tan θ)° with background counts of 15-s duration on either side of the peak. The intensities were corrected for Lorentz and polarization factors but not for absorption. Altogether, 3128 reflections were measured, and, of these, 2524 reflections with $|F_o| > 3\sigma(F_o)$ were considered observed and used for the structure determination.

The structure was solved by direct methods using the program MULTAN 78[18] and refined by the block-diagonal least-squares method with anisotropic temperature factors for all the nonhydrogen atoms and with isotropic ones for the hydrogen atoms. The final residual index R was 0.043 and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$ was 0.066. The weighting scheme used in the final least-squares cycle was $1/w = a + |F_o| + c|F_o|^2$, where $a = 2F_o$ (min) and $c = 2/F_o$ (max). The final difference Fourier map was featureless. Figure 1 was drawn with local version of the ORTEP-II program.[19]

Acknowledgment. We are indebted to Professors Sigeru Torii and Kenji Uneyama of Okayama University for measurement of 100-MHz ^{1}H NMR spectra and for their generous advice. We also thank Hideo Naoki and Dr. Tsutomu Sakai, Suntory Institute for Bioorganic Research, for measurement of 360-MHz ^{1}H NMR spectra and for their helpful discussions, and Mr. Azusa Yoshioka of our laboratory for obtaining HRMS spectra.

Supplementary Material Available: Tables of fractional coordinates, temperature factors, bond distances, and bond angles for keto ester 13 (5 pages). Ordering information is given on any current masthead page.

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Two Total Syntheses of Showdomycin and Related Studies

Anthony G. M. Barrett* and Howard B. Broughton

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Steven V. Attwood and A. A. Leslie Gunatilaka

Department of Chemistry, Imperial College, London SW7 2AY, England

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After a series of model reactions, D-ribose (2) was reacted with 3-(triphenylphosphoranylidene)-2,5-pyrrolidinedione (**8a**) in THF at reflux to produce 3(*E*)-(2(*S*),3(*S*),4(*R*),5-tetrahydroxy-1-pentylidene)-2,5-pyrrolidinedione (**35**) (75%). Subsequent cyclization of **35** using phenylselenenyl chloride followed by hydrogen peroxide gave showdomycin (**1**) (13%) and *epi*-showdomycin (**36**) (41%). Using a similar strategy 2,3-*O*-isopropylidene-D-ribose (**37b**) was reacted sequentially with 1-(triphenylmethyl)-3-(triphenylphosphoranylidene)-2,5-pyrrolidinedione (**8b**), phenylselenenyl chloride, hydrogen peroxide, and trifluoroacetic acid to give 1 (3% overall).

Showdomycin (1) was first isolated from *Streptomyces showdoensis* by Nishimura et al. of the Shionogi Research Laboratory.[1] This C-glycoside is noted both for its antibiotic activity, especially against *Streptococcus hemolyticus*, and for its inhibition of Ehrlich ascites tumors in mice.[2] Several successful multistage total syntheses of 1 have been reported by using either protected carbohydrates including ribose[3-6] or furan–dienophile cycloadducts[7] as starting materials. Without exception, in these syntheses, the maleimide ring of 1 was introduced indirectly either via carbacyclic or acyclic β-anomeric substituents on the ribose ring. In addition only one synthesis[3] prior to our preliminary publication[8] produced the C-9 skeleton of 1 directly in the first step. Herein we report experimental details for the total synthesis of 1 by a two-step protocol and by a four-step protocol. In addition, synthetic studies on conceptually similar but unsuccessful routes will be summarized.

In principle showdomycin (1) should be available in one step from the condensation reaction of D-ribose (2) with a maleimide anion equivalent (3) or from δ-D-ribonolactone (**4a**)[9] and a succinimide anion equivalent (5). In addition

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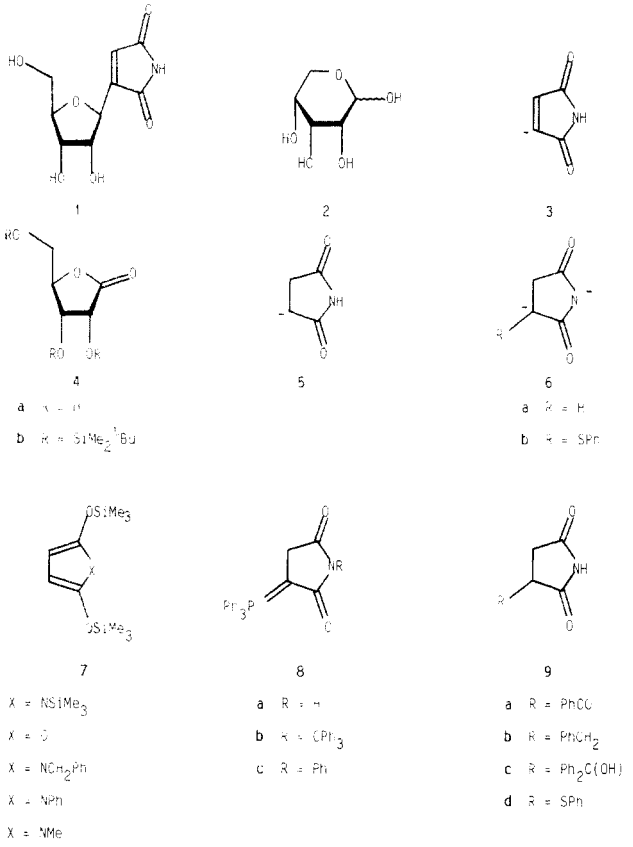
0022-3263/86/1951-0495$01.50/0

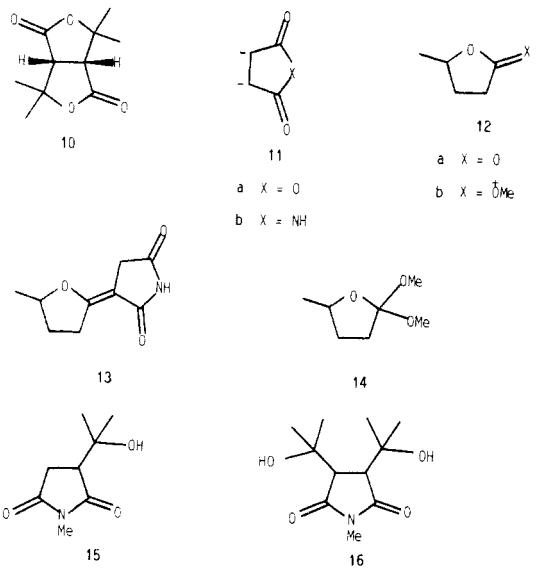
there are two possible two-step syntheses of **1** corresponding to the **2** plus **5** and the **3** plus **4a** condensations followed by redox manipulations. Dianion **6**, pyrrole **7a**, and ylide **8** were each examined as potential reagents for showdomycin (**1**) synthesis.



Results and Discussion

Preparation and Reactions of Dianion 6. Hauser and co-workers[10] have demonstrated that **6a**, which was produced from the deprotonation of succinimide with potassium amide, readily condensed with methyl benzoate, benzyl chloride, or benzophenone to produce **9a–c** (29–66%). Following this precedent, we set out to study the condensation reaction of **6a** with **4b**.[11] Thus succinimide was converted into **6a** by using potassium hexamethyldisilazide in THF–1,2-dimethoxyethane and condensed with **4b**. Unfortunately, only complex mixtures of unstable products resulted. In an attempt to moderate the basicity of **6a** we sought to prepare the phenylthio derivative **6b**. Dianion **6a** smoothly reacted with diphenyl disulfide to produce **9d** (50%). However, all attempts to metalate **9d** to produce **6b** resulted in extensive decomposition. Thus the attempt to prepare **1** from **6** was abandoned.

Preparation and Reactions of Pyrrole 7a. Simchen and co-workers have reported the synthesis of 1-(trimethylsilyl)-2,5-bis[(trimethylsilyl)oxy]pyrrole (**7a**) and related compounds from the reaction of succinimide with trimethylsilyl trifluoromethanesulfonate and triethylamine.[12] Previously Chan converted succinic anhydride into **7b** using chlorotrimethylsilane and condensed **7b** inter alia with acetone in the presence of titanium tetrachloride to efficiently produce **10**.[13] Clearly **7b** in this reaction is



functioning as a synthetic equivalent for dianion **11a**. Thus, in principle, **7a** should be able to function as an equivalent for dianion **11b** or monoanion **5** depending upon the reaction conditions.

Succinimide, *N*-benzylsuccinimide, and *N*-phenylsuccinimide were converted into crude **7a**[12] (92%), **7c** (95%), and **7d**[12] (71%) by using trimethylsilyl trifluoromethanesulfonate and triethylamine. None of these reactive pyrroles could be obtained microanalytically pure and all were used directly. Lactone **12a** was condensed with **7a** in the presence of titanium tetrachloride to produce **13** (1%). No other products could be isolated from the intractable reaction mixture. In addition the use of alternative Lewis acids and/or the pyrroles **7c** or **7d** were even less successful! Following the Yoshimura precedent[14] lactone **12a** was converted into the ortho lactone **14**. We anticipated that this should generate **12b** in the presence of a Lewis acid. Thus **14** was condensed with **7a** in the presence of trimethylsilyl trifluoromethanesulfonate to produce the same adduct **13** in poor yield (2%). Again no other products were identified from the intensely purple colored reaction mixture.

It is interesting to note that Lozzi et al.[15] efficiently converted **7e** into **15** (91%) or **16** (64%) by using tin(IV) chloride and acetone in the appropriate stoichiometry. Since the condensation of **7a** with the simple lactone **12a** proceeded in such abysmal yields the reaction of **7a** with **4b** was not investigated.

Condensation of Ylide 8a with D-Ribose (2) and Related Reactions. In 1968 Hedaya and Theodoropulos[16] reported that triphenylphosphine reacted with maleimide in acetic acid to produce the ylide **8a** (~100%). This reacted with benzaldehyde to produce **17** (77%). In addition **8a** and related ylides were successfully condensed in the same way with diverse aldehydes. In a reaction that is particularly auspicious for the extension of ylide **8a** to lactol functionalization, Hedaya et al. reported that **8c** reacted with **18** in acetic acid as solvent to provide **19** (50%). In 1969–1970 Harmon et al.[17] reported their

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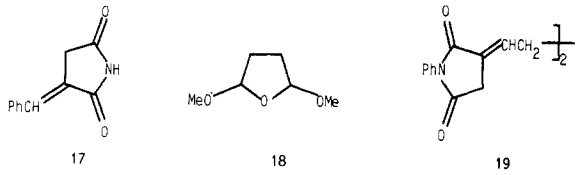
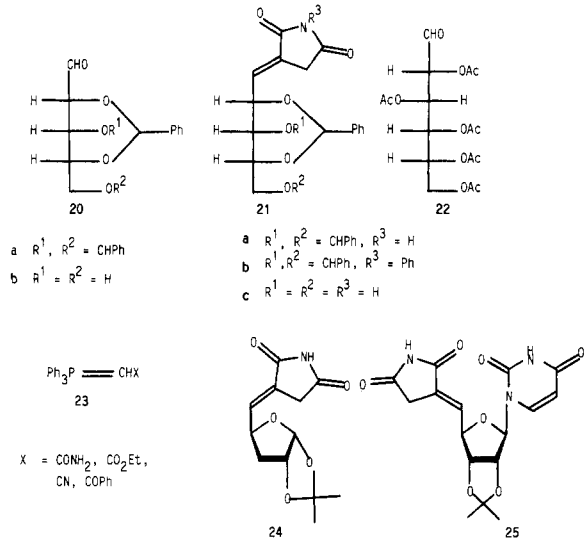


17 18 19

studies on the reactions of **8a** and **8c** with *aldehydo*-D-ribose and -D-glucose derivatives. Although the reactions of **20a** with **8a** or **8c** or of **20b** with **8a** in ethanol solution successfully provided the appropriate Wittig adducts **21a**, **21b**, and **21c**, the *aldehydo*-glucose derivative **22** gave only intractable mixtures on reaction with either ylide. In contrast both **20a** and **22** were condensed efficiently with the acyclic ylides **23**. Clearly Harmon et al. realized the potential of **8a** for showdomycin (**1**) synthesis. However, any studies by that group on the conversion of **21** into showdomycin (**1**) have not been published. In 1979



20 21 22

a R^1, R^2 = CHPh
b $R^1 = R^2$ = H

a R^1, R^2 = CHPh, R^3 = H
b R^1, R^2 = CHPh, R^3 = Ph
c $R^1 = R^2 = R^3$ = H

$Ph_3P{=}CHX$

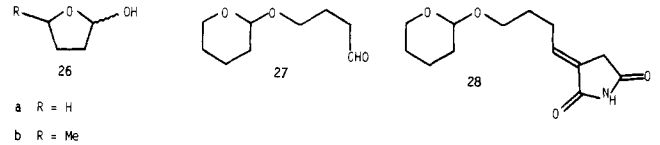
23

X = $CONH_2$, CO_2Et, CN, COPh

24 25

Tronchet et al. extended Harmon's work on the condensation reactions of **8a** with protected *aldehydo* sugars and used the method to prepare with high *E* selectivity several substituted succinimides including **24** and **25**.[18] In light of these specific reports and also the numerous successful condensations reactions between stabilized phosphoranes **23** and lactols,[19] we were optimistic as to realizing the direct synthesis of showdomycin (**1**) from ylide **8a** and D-ribose (**2**).

Initially, however, we examined several model systems. 4-(2-Tetrahydropyranyloxy)butanal (**27**)[20] reacted slowly (48 h) with the ylide **8a** in methanol solution to provide **28**. The yield was poor, however, on account of difficulty

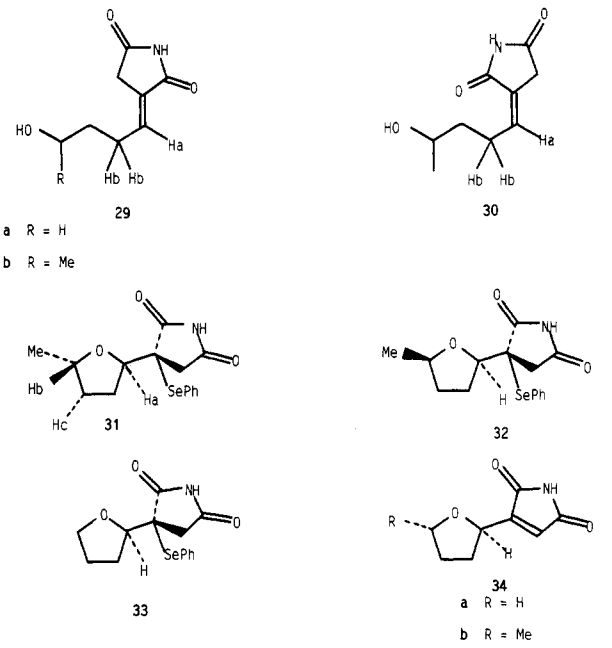


26 27 28

a R = H
b R = Me

in separating the product from triphenylphosphine oxide.

A sample of **28** contaminated with Ph_3PO was hydrolyzed under acidic condition to provide **29a** (38%). In acetic acid containing traces of water the lactol **26a** condensed with ylide **8a** to give the same *E*-substituted succinimide derivative **29a** (40%). The preparation of neither **28** nor **29a** was optimized. However, the reaction between **8a** and lactol **26b** was studied in more detail. At approximately 0.6 M concentration **8a** and **26b** reacted together in wet acetic acid over 65 h to provide **29b** (83%). In a subsequent experiment small quantities of the *Z* isomer **30** (8%) were isolated in addition to **29b** (68%). The two isomers were readily distinguished by their respective NMR spectra[21] [**29b** δ 6.55 (tt, 1 H, *J* = 8, 2 Hz, Ha), 2.30 (br q, 2 H, *J* = 8 Hz, Hb) and **30** δ 5.95 (tt, *J* = 8, 2 Hz, Ha), 2.5 (br q, 2 H, *J* = 8 Hz, Hb)]. The succinimide derivative **29b** was also prepared from **8a** and **26b** in wet acetonitrile containing 4% acetic acid (28%) or in wet methanol containing 2% acetic acid (32%) or in methanol (8%). The condensation reaction, however, failed in DMF, Me_2SO, acetonitrile, or chloroform in the absence of acetic acid.



29 30

a R = H
b R = Me

31 32

33

34

a R = H
b R = Me

Nicolaou and others[22,23] have demonstrated the versatility of the selenoetherification reaction in organic synthesis. Thus following this excellent precedent **29a** and **29b** were reacted with phenylselenenyl chloride in acetonitrile solution to produce **31** (80%) and **32** (5%) or **33** (93%). The stereochemistry of **31**, and by inference **32**, was determined by a difference nuclear Overhauser effect experiment. Thus irradiation of the methyl doublet at δ 1.19 resulted in only three protons showing major Overhauser enhancements in the difference spectrum. These protons were Ha (δ 4.55), Hb (δ 4.18), and Hc (δ 1.56). Clearly the ring methyl substituent in **31** was cis with respect to both Ha and Hc.

Following well-established selenium chemistry[24] **31** was oxidized with hydrogen peroxide or ozone to efficiently provide, via the selenoxides and syn elimination, the maleimide derivative **34b** (99%, 95% respectively). In addition **33** was converted into **34a** (100%) via ozonation. In

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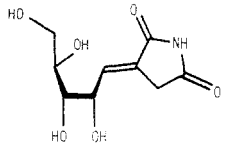
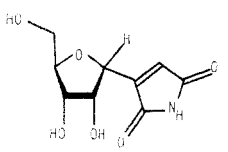
(24) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049.

both the conversion of **31** into **34b** and of **33** into **34a** the elimination of the intermediate selenoxide was regiospecific in that, for example, **13** was not obtained as a byproduct. In general selenoxide elimination reactions toward heteroatoms to produce vinyl ethers, etc., are inefficient.[25,26]

Encouraged by these model studies we sought to extend the chemistry to D-ribose (**2**). However, Harmon et al.[17] in 1969 reported that "Attempts to cause unprotected D-ribose and D-glucose to react directly with the ylides" **8a** and **8c** "were unsuccessful". In our hands, ylide **8a** was found to smoothly, albeit slowly, react with D-ribose (**2**) in THF at reflux to produce **35** (75%). This was obtained



35



36

exclusively as the *E* isomer (NMR spectrum). The condensation reaction also proceeded cleanly in acetonitrile, acetone, or 1,2-dimethyoxyethane at reflux (30–57%) but not cleanly in acetic acid (anhydrous or wet). Of crucial importance in monitoring the progress of the reaction was the use of reverse phase C-18 TLC plates developed in water, which readily resolved **2**, **8a**, and **35**. Subsequent to the preliminary publication of our results[8] Wellman stated that their failure to observe reaction between ylide **8a** and D-ribose (**2**) referred to brief reaction in ethanol or DMF only.[27]

Reaction of **35** with phenylselenenyl chloride in acetonitrile at 65 °C for 29 h followed by hydrogen peroxide oxidation and selenoxide elimination in situ gave a mixture of showdomycin (**1**) and *epi*-showdomycin (**36**) (80%). These were separated on a modest scale by reverse phase HPLC on Dupont Zorbax ODS to provide **1** (13%) and **36** (41%). The structures of **1** and **36** were unequivocally confirmed by comparisons with authentic samples[28] and by an X-ray crystallographic study of **36**.[8] Clearly since the selenoetherification reaction gave rise only to **1** and **36** rather than the isomeric pyranose derivatives the cyclization was subject to kinetic control.[22]

The selenoetherification reaction was alternatively carried out at a lower temperature (0 °C) when the combined yield of **1** and **36** was reduced (61%) but the ratio remained unchanged (1:3 by HPLC). We extensively examined the selenoetherification–selenoxide elimination reaction under a range of conditions. In the solvents THF, isopropyl alcohol, trimethyl borate, or DMF reaction gave mixtures (generally 1:3 to 1:6 by HPLC) of **1** and **36** (0–99%). In contrast to our preliminary publication,[8] which contains an error, the optimum preparative synthesis of showdomycin (**1**) and *epi*-showdomycin involved the use of acetonitrile rather than trimethyl borate as solvent for the cyclization of **35**.

While our studies were in progress, Mann reported[4] the completion of a formal total synthesis of showdomycin (**1**) using as key steps the reaction of **37** with **38** to produce **39** and its subsequent cyclization mediated by phenylselenenyl chloride followed by ozone to produce **40**. This work is especially interesting in that the **39** to **40** conversion was achieved with excellent stereoselectivity. Presumably preferential formation of the β-anomer **40** resulted from severe steric congestion in the intermediate **41** (which gives rise to the α-anomer) relative to the β-diastereoisomeric intermediate **42**. In addition such differentiation between the two intermediates would only be large when O-2 and O-3 (ribose numbering) were eclipsed as in the isopropylidene derivative. In a series of definitive papers, Moffatt previously reported that **37b** and related lactols reacted with stabilized ylides in acetonitrile as solvent to produce **43** (X = CO_2Et, CN, etc.) with excellent anomeric selectivity (β:α 22–50:1).[29] Clearly in the cyclization of **35** to produce **36** and **1** the β:α selectivity is dramatically reduced on account of O-2 and O-3 not being eclipsed and the α-face not being shielded. We therefore sought to improve our methodology by examining isopropylidene derivatives of **35**.

2,3-*O*-Isopropylidene-D-ribose (**37b**)[30] reacted smoothly with ylide **8a** optimally in 1,2-dimethoxyethane at 60 °C for 290 h to produce (*E*)-**44a** (52%). Reactions in THF (13%) or chloroform (15%) were less efficient. Although the preparation of **44a** was straightforward, its oxidative cyclization with phenylselenenyl chloride in acetonitrile at 0 °C for 60 h gave only showdomycin (**1**) and *epi*-showdomycin **36** (1:3). Under these conditions loss of the isopropylidene protecting group preceded the slow selenoetherification. Alternatively, the reaction of **44a** with phenylselenenyl chloride in the presence of base ($NaHCO_3$ or 2,6-di-*tert*-butylpyridine) gave intractable mixtures. It is reasonable to assume that the mildly basic reaction conditions were complicated by N-phenylselenenylation.[31] Such a problem would be circumvented by the aesthetically unappealing option of global protection.

Reaction of triphenylphosphine with 1-(triphenylmethyl)-1*H*-pyrrole-2,5-dione[32] gave the ylide **8b** (100%). This ylide **8b**, generated in situ, reacted extremely slowly with **37b** to produce after 10 days the expected product **44b** and its geometric isomer **45** (30%, ca. 5:3). Incomplete reaction accounted for the low yield and starting material **37b** (68%) was also recovered. Attempts to accelerate the reaction at higher concentrations or temperatures resulted in extensive decomposition. The formation of substantial quantities of the *Z* isomer **45** in the reaction is both inconsistent with all our previous observations and mechanistically puzzling. The mixture of geometric isomers **44b** and **45** were cyclized extremely slowly under the Mann conditions.[4] Thus reaction with excess phenylselenenyl chloride and anhydrous potassium carbonate in dichloromethane gave **46** (17%) along with recovered unreacted starting material **44b** and **45** (60%). The stereochemistry of the product at C-1′ (showdomycin numbering) was unequivocally established by a difference nuclear Overhauser effect experiment. Thus in the NOE experiment irradiation at δ 4.15 (d, 1 H, J = 4.3 Hz, H-1′) resulted in an enhancement of the signal at δ 3.85 (m, 1 H, H-4′) in the difference spectrum. The stereochemical assignment was confirmed by the subsequent conversion of **46** into showdomycin (**1**). Hydrogen peroxide oxidation of **46** gave **47** (76%) and this was doubly deprotected by reaction with wet trifluoroacetic acid to produce showdomycin (**1**) (87%). The choice of deprotection conditions was guided by preliminary experiments on the hydrolysis of *N*-trityl-

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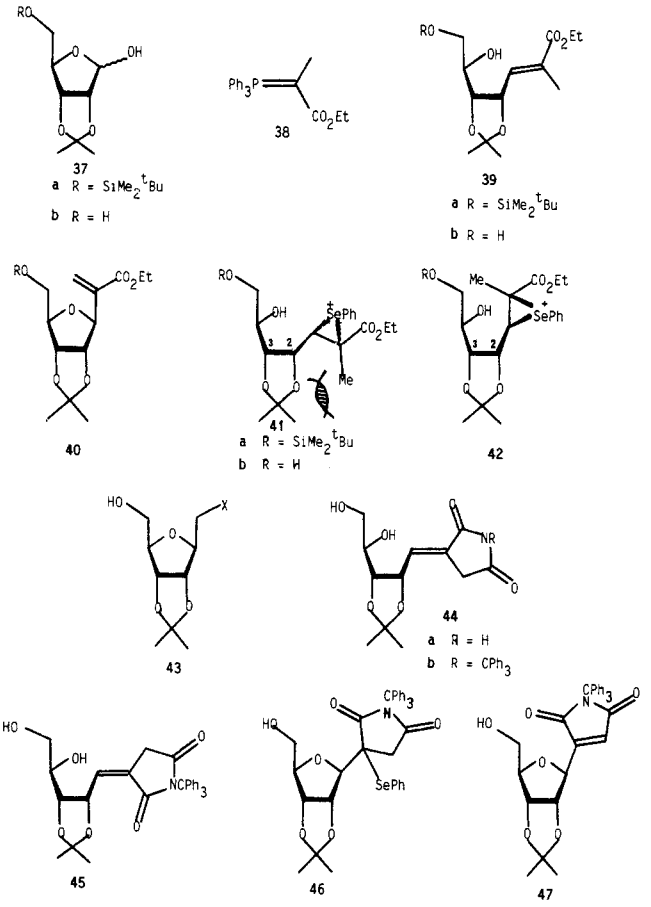

maleimide to produce maleimide (65%).

Conclusions

We have developed two total syntheses of showdomycin starting from D-ribose. The first synthesis is notably brief (two steps) and does not require the use of classical hydroxy group protection. While the first step in the synthesis, the condensation reaction of D-ribose (**2**) and ylide **8a** was highly *E* stereoselective and efficient (75%) on a large scale, the oxidative cyclization of the product **35** to produce showdomycin (**1**) (13%) was complicated by the coproduction of *epi*-showdomycin (**36**) (41%). This necessitated an HPLC separation. In the second synthesis 2,3-*O*-isopropylidene-D-ribose (**37b**) was reacted sequentially with ylide **8b**, phenylselenenyl chloride, hydrogen peroxide, and trifluoroacetic acid. Although only showdomycin (**1**) was produced by this protocol, the synthesis has the disadvantage of poor conversions. If limited quantities (~ mmol) of showdomycin (**1**) are required the two-step synthesis via **35** and HPLC separation can be recommended for its simplicity.

Experimental Section

Melting points were recorded on a Kofler or Reichert-Thermover hot stage instrument and are uncorrected. Microanalyses were carried out at Imperial College, London, or by Galbraith Laboratories Inc., Knoxville, TN. Organic extracts were dried over anhydrous sodium or magnesium sulfate and were concentrated by rotary evaporation. Chromatography refers to "Flash Chromatography" on Merck 9385 intermediate grade silica gel. Reverse phase chromatography was carried out on C18 modified merck 9385 silica gel. This was prepared as follows: dried (250 °C, 24 h) silica gel (1 kg) was washed sequentially with octadecyltrichlorosilane (100 g) in dry PhMe (2.5 L) for 24 h, dry toluene (2.5 L), and MeOH (5 × 2 L, 1 L) and dried (24 h, 60 °C, 1 mm).

3-(Phenylthio)-2,5-pyrrolidinedione (9d) (With Peter Quayle). Lithium diisopropylamide, from MeLi (1.2 M; 5 mL), THF (10 mL) and *i*-Pr_2NH (0.84 mL), was added to dry succinimide (0.199 g) in THF (20 mL) at −78 °C. After 1 h at −78 °C the solution was allowed to warm up to −50 °C and recooled at −78 °C and PhSSPh (0.42 g) in THF (5 mL) added. The solution was allowed to warm to −20 °C and recooled to −78 °C and quenched with HOAc (0.314 mL). After evaporation the residue was dissolved in CH_2Cl_2 (30 mL) and washed with H_2O (2×) and saturated aqueous NaCl, dried, and evaporated. Chromatography gave unreacted PhSSPh (134 mg) (eluant CH_2Cl_2) and **9d** (205 mg, 50%) (eluant Et_2O): mp 93.5–94.5 °C (from Et_2O); IR ($CDCl_3$) 3410, 1790, 1740, 1150 cm^{-1}; ^1H NMR δ 8.5 (s, 1 H, NH), 7.6 (m, 5 H), 4.15 (dd, 1 H, *J* = 9, 5.5 Hz), 3.25 (dd, 1 H, *J* = 9, 18 Hz), 2.75 (dd, 1 H, *J* = 5.5, 18 Hz); mass spectrum, *m/e* 207 ($M^{+\cdot}$), 136, 135, 110, 109. Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.93; H, 4.38; N, 6.76. Found: C, 57.84; H, 4.89; N, 6.49%.

1-(Trimethylsilyl)-2,5-bis[(trimethylsilyl)oxy]pyrrole (7a). Trimethylsilyl trifluoromethanesulfonate (6.2 g) was added dropwise to a stirred solution of Et_3N (3.64 g) in 1,2-dimethoxyethane (25 mL) at −23 °C. The mixture was treated with a solution of succinimide (0.99 g) in 1,2-dimethyoxyethane (10 mL) and stirred at −23 °C for 3.5 h. The solution was poured into cold (0 °C) dry pentane (100 mL) and the red, oily lower phase was separated. Extraction of the lower phase with a further portion of pentane (100 mL) gave, on evaporation of the combined pentane extracts, the crude pyrrole **7a** contaminated with *N*-(trimethylsilyl)succinimide (NMR). The latter separated from a pentane (25 mL) solution of the crude products on standing overnight at −18 °C to give the pyrrole **7a** free of contaminants by ^1H NMR spectroscopy (2.7 g, 92%). A portion (1 g) of this was distilled to give pure **7a** (0.35 g, 32%): bp 95 °C (0.8 mmHg) (lit.[12] bp 67 °C (0.01 mmHg)); IR (neat) 2983, 1575, 1555, 1320, 1267, 1130, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $NSi(CH_3)_3$), 0.19 (s, 18 H, $OSi(CH_3)_3$), 4.64 (s, 2 H, —CH=); mass spectrum, *m/e* 315 ($M^{+\cdot}$), 300 (M^+ − Me), 242 (M^+ − Me_3Si), 156 (base peak, O:C:CHCH:C:O^+SiMe_3 + 1); exact mass calcd for $C_{13}H_{29}NO_2Si_3$ ($M^{+\cdot}$) 315.1506, found ($M^{+\cdot}$) 315.1505.

***N*-Benzyl-2,5-bis[(trimethylsilyl)oxy]pyrrole (7c).** Trimethylsilyl trifluoromethanesulfonate (4.04 g) was added dropwise at −23 °C to a stirred solution of Et_3N (2.4 g) in Et_2O (15 mL). The resulting suspension was treated with a solution of *N*-benzylsuccinimide (1.89 g) in Et_2O (20 mL) and the mixture stirred at −23 °C for a further 3 h. The product was isolated as described for pyrrole **7a** to give the pyrrole **7c** as a yellow oil (3.05 g, 95%), contaminated (^1H NMR) with a small amount of starting succinimide. This oil was subject to decomposition at temperatures above 45 °C and could not be distilled at pressures down to 10^{-4} mmHg. The product mixture showed the following spectral properties: IR (neat) 3060, 3030, 2955, 1570, 1250, 1060, 855, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.2 (s, 18 H, $OSi(CH_3)_3$), 5.7 (s, 2 H, —CH=), 5.9 (s, 2 H, $PhCH_2$), 7.1 (m, 5 H); mass spectrum, *m/e* 333 ($M^{+\cdot}$), 242 (M^+ − $PhCH_2$), 147, 91, 73.

***N*-Phenyl-2,5-bis[(trimethylsilyl)oxy]pyrrole (7d).** *N*-Phenylsuccinimide (1.4 g) was dissolved in 1,2-dimethoxyethane (20 mL) and treated with Et_3N (3.17). The mixture was cooled to −23 °C, treated with trimethylsilyl trifluoromethanesulfonate (3.55 g), and stirred at −23 °C for a further 6 h. Approximately half the solvent was evaporated (rotary evaporator, 28 mmHg, bath temperatures less than 60 °C) and the mixture was poured into cold dry pentane (100 mL). The product was purified as described for pyrrole **7a**. The resulting yellow oil was distilled to give the desired pyrrole **7d** (1.8 g, 71%) as a yellow oil: bp 84 °C (5×10^{-5} mmHg) (lit.[12] bp 97 °C (4×10^{-2} mmHg)); ^1H NMR ($CDCl_3$) δ 0.0 (s, 18 H, $OSi(CH_3)_3$), 5.0 (s, 2 H, —CH=), 7.4 (br s, 5 H); a small signal (s, <1 H) at δ 2.8 was assigned to contaminating *N*-phenylsuccinimide.

Condensation of Pyrrole 7a with Lactone 12a in the Presence of Titanium Tetrachloride. A solution of pyrrole **7a** (3.15 g) and lactone **12a** (1.0 g) in CH_2Cl_2 (10 mL) was cooled to −78 °C and treated dropwise with $TiCl_4$ (0.95 g). The mixture was stirred at −78 °C for a further 4 h and then allowed to warm to 0 °C and poured into 1 M HCl (100 mL). Extraction with CH_2Cl_2 (3 × 50 mL), drying of the combined organic extracts, and evaporation gave a light yellow oil (1.06 g) which was subjected to column chromatography (silica gel–Et_2O) to give first recovered

lactone **12a** (0.5 g) and lactone **12a** contaminated with a small amount of solid material which appeared on TLC analysis (silica gel, $CHCl_3$–MeOH, 9:1) to be the desired product. Recrystallization from MeOH (3 times) afforded a white crystalline solid (18 mg, 1%): mp 212–214 °C, UV (CH_2Cl_2) λ_{max} 258 nm (log ϵ = 4.46). This material had identical spectral properties with those observed for the condensate **13** (see below) but failed to analyze correctly.

2,2-Dimethoxy-5-methyltetrahydrofuran (14). A mixture of lactone **12a** (1 g) and $MeOSiMe_3$ (2 g) was dissolved in dry $CHCl_3$ (10 mL) and cooled to −23 °C. The stirred solution was treated with trimethylsilyl trifluoromethanesulfonate (100 mg) and allowed to warm to room temperature. After a period of 2 days the reaction had ceased (^{1}H NMR). The mixture was treated with a solution of NaOMe (25 mg) in tetrahydrofuran (1 mL). Distillation of the residue gave the desired ortho lactone **14** as a colorless oil (0.6 g, 41%): bp 60 °C (10 mmHg); IR (neat) 2980, 1455, 1440, 1380, 1315, 1220, 1170, 1082, 1043, 982, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.20 (m, 1 H, HCO–), 3.29 (s, 3 H, OCH_3), 3.27 (s, 3 H, OCH_3), 1.60–2.20 (m, 4 H, -CH_2-), 1.28 (d, 3 H, J = 6.2 Hz, CH_3); mass spectrum, m/e 146 ($M^{+\cdot}$), 131 (M^+ − Me), 115 (M^+ − MeO).

Condensation of Pyrrole 7a with Lactone Derivative 14: 3-(5-Methyl-2-tetrahydrofuranylidene)-1*H*-pyrrole-2,5-dione (13). A stirred solution of pyrrole **7a** (3.15 g) and lactone derivative **14** (1.46 g) in $CHCl_3$ (25 mL) was treated dropwise at −23 °C with trimethylsilyl trifluoromethanesulfonate (0.222 g). The mixture was stirred at this temperature for a further 8 h, warmed to room temperature, and stirred overnight. The reaction was allowed to stand for 2 days at room temperature and was then treated with a solution of MeOH (1 mmol) and pyridine (1 mmol) in chloroform (1 mL). Partitioning of the products between $CHCl_3$ (50 mL) and H_2O (50 mL), followed by extraction of the aqueous phase with $CHCl_3$ (3 × 50 mL), gave, after drying and evaporation of the combined organic extracts, a purple paste: UV λ_{max} 258 nm (log ϵ = 3.9). Flash chromatography on silica gel with Et_2O as eluant afforded white crystals which were sublimed at 160 °C to give the desired imide (**13**) as white needles (40 mg, 2%): mp (sealed tube) 228–30 °C; UV (EtOH) λ_{max} 205 (log ϵ = 4.17), 261 (log ϵ = 4.45); IR ($CHCl_3$) 1720, 1673; IR (Nujol) 3400, 1760, 1710, 1645, 1100, 1030, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.57 (br s, 1 H, NH), 4.62 (m, 1 H, H^5), 3.36 (m, 1 H, H^3), 3.26 (2 d, 2 H, J = 1.4 Hz, O=CCH_2), 3.0 (m, 1 H, H^3), 2.29 (m, 1 H, H^4) 1.71 (m, 1 H, H^4), 1.40 (d, 3 H, J = 6 Hz, CH_3); mass spectrum, m/e 181 ($M^{+\cdot}$), 163, 152, 138. Anal. Calcd for $C_9H_{11}NO_3$: C, 59.61, H, 6.12; N, 7.73. Found: C, 59.57, H, 6.12; N, 7.67%.

2-Hydroxy-5-methyltetrahydrofuran (26b). The title compound was prepared by an adaptation of a method described by CIBA Ltd.[34] A stirred solution of diisobutylaluminum hydride (32% w/w, 59.25 mL) in PhMe was cooled to −78 °C and treated dropwise with a solution of lactone **12a** (10.4 g) in PhMe (10 mL) over a period of 0.5 h. Stirring at −78 °C was continued for a further 3 h, and the mixture was treated with HOAc (20.2 mL) over the course of 1 h, the internal temperature being held below −50 °C. The mixture was allowed to warm to 0 °C and treated dropwise with H_2O (6 mL). Solid $NaHCO_3$ (40 g) was then added in small portions (to minimize frothing) and the resulting white paste extracted with EtOAc (7 × 100 mL). The combined extracts were dried, evaporated, and distilled to give a 1:1 diastereoisomeric mixture (^{1}H NMR) of the desired lactol **26b** (9.23 g, 87%) as a colorless oil: bp 108–115 °C (23 mmHg), (lit.[34] bp 66–68 °C (12 mmHg)); IR (neat) 3495, 2980, 1722, 1660, 1460, 1385, 1200, 990, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.45 (m, 1 H, OCHO), 4.15 (m, 1 H, CHO), 4.0 (br s, 1 H, exchangeable, OH), 1.5–2.5 (m, 4 H), 1.3 (d, 1.5 H, J = 9 Hz, cis-CH_3), 1.2 (d, 1.5 H, J = 9 Hz, trans-CH_3). A small signal at δ 9.7 (s) was assigned to the CHO proton of the open-chain form of this compound.

2-Hydroxytetrahydrofuran (26a). Butyrolactone (3.0 g) was reduced with diisobutylaluminum hydride following the procedure described above for the preparation of **26b**. Distillation gave the desired lactol **26a** (1.6 g; 52%) as a clear oil: bp 95 °C (18 mmHg), (lit.[35] bp 65 °C (12 mmHg)); IR (neat) 3415, 2930, 1440, 1340, 1190, 975, 865, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.48 (br s, 1 H, OCHO), 4.95 (br s, 1 H, OH), 3.3–4.3 (m, 2 H, OCH_2), 1.5–2.2 (m, 4 H).

3-(Triphenylphosphoranylidene)-2,5-pyrrolidinedione (8a). The title compound was prepared by the method of Hedaya and Theodoropoulos,[16] except that acetone was used as the solvent and **8a** was isolated (92%) as white crystals: mp 211–221 °C dec (lit.[16] mp 220 °C).

3(*E*)-(4-Hydroxybutylidene)-2,5-pyrrolidinedione (29a). Method A: A Two-Step Procedure. A stirred suspension of ylide **8a** (360 mg) in MeOH (20 mL) was treated dropwise with a MeOH (1 mL) solution of the protected hydroxy aldehyde **27**[20] (172 mg). The mixture was stirred at room temperature for 48 h, the solvent evaporated, and the residue subjected to column chromatography (silica gel; $CHCl_3$ to $CHCl_3$–MeOH, 9:1) to give the protected (4-hydroxybutylidene)succinimide **28** (85 mg, 34%) as a light brown syrup, preceded by a fraction consisting of **28** mixed with triphenylphosphine oxide (440 mg), also as a light brown syrup. The latter appeared (^{1}H NMR) to contain approximately 160 mg (63%) of **28** and was used in the second step of this preparation without further purification. The tetrahydropyran derivative **28** showed the following spectral properties: IR (neat) 3550, 3210, 2980, 1770, 1730, 1680, 1350, 1290, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.3 (br s, 1 H, NH), 6.75 (tt, 1 H, J = 2.5, 8 Hz, =CH—), 4.5 (br s, 1 H, OCHO), 3.55 (m, 4 H, OCH_2), 3.25 (d, 2 H, J = 2.5 Hz, O=CCH_2), 2.3 (br q, 2 H, J = 8 Hz, =CCH_2), 1.65 (m, 8 H); mass spectrum, m/e 255 (M^+ + 2), 169 (M^+ − C_5H_9O + 1), 85 ($C_5H_9O^+$). The mixture of protected (4-hydroxybutylidene)succinimide **28** and triphenylphosphine oxide prepared above (440 mg) was dissolved in THF (5 mL) and treated with H_2O (1 mL) and Amberlite IR 120-H^+ resin (0.5 g). The reaction was stirred at room temperature overnight and filtered, and the solvent was evaporated. Chromatography on silica gel ($CHCl_3$ to $CHCl_3$–MeOH, 9:1) and recrystallization from EtOAc gave the (hydroxyalkylidene)succinimide **29a** (41 mg, 38%) as white crystals: mp 109–110 °C; IR ($CHCl_3$) 3600, 2900, 1770, 1720, 1675, 1525 cm^{-1}; ^{1}H NMR ($(CD_3)_2CO$) δ 9.9 (br s, 1 H, NH), 6.63 (tt, 1 H, J = 2, 8 Hz, =CH), 3.6 (t, 2 H, J = 4 Hz, OCH_2), 3.3 (d, 2 H, J = 2 Hz, O=CCH_2), 2.9 (br s, 1 H, OH), 2.35 (m, 2 H, =$CHCH_2$), 1.7 (m, 2 H, —CH_2—); mass spectrum, m/e 169 ($M^{+\cdot}$), 151 (M^+ − H_2O). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.40; H, 6.51; N, 8.28. Found: C, 56.64; H, 6.57; N, 8.14%.

Method B: A One-Step Procedure. To a stirred solution of **8a** (3.59 g) in HOAc (5 mL) was added a 17% w/v solution of the lactol **26a** (440 mg) in HOAc dropwise at room temperature. The mixture was treated with H_2O (180 μL), stirred for 65 h, and monitored by TLC ($CHCl_3$–MeOH, 9:1) and ^{1}H NMR spectroscopy (signals at δ 3.1 in **8a** and at δ 3.3 in **29a** were compared). The reaction was worked up by evaporation of all volatile material and flash chromatogaphy of the products ($CHCl_3$–MeOH, 9:1, as eluant). The desired product **29a** was finally purified by recrystallization from EtOAc to give white crystals of **29a** (238 mg, 40%), showing physical data identical with those obtained for material prepared by method A above.

3(*E*)-(4-Hydroxypentylidene)-2,5-pyrrolidinedione (29b). To a stirred solution of **8a** (3.59 g) in HOAc (5 mL) was added a 17% w/v solution of the lactol **26b** (510 mg) in HOAc, dropwise at ambient temperature. The mixture was treated with H_2O (180 μL) and stirred for 65 h. The reaction was monitored by TLC ($CHCl_3$–MeOH, 9:1) and worked up by evaporation of all the volatile material and chromatography of the residue as described for **29a**. Recrystallization from EtOAc gave the (hydroxyalkylidene)succinimide **29b** (1.52 g, 83%) as white crystals: mp 112–113 °C; UV λ_{max} 230 nm (log ϵ = 3.89); IR (Nujol) 3400, 3140, 3050, 1760, 1710, 1680; IR (CH_2Cl_2) 3620, 3410, 2940, 1780, 1730, 1680, 1340, 1176, 1050 cm^{-1}; ^{1}H NMR (90 MHz, $(CD_3)_2CO$) δ 10.0 (br s, 1 H, NH), 6.55 (tt, 1 H, J = 2.5, 8 Hz, =CH), 4.2 (br s, 1 H, OH), 3.76 (m, 1 H, —CHOH), 3.1 (d, 2 H, J = 2.5 Hz, O=CCH_2), 2.30 (br q, 2 H, J = 8 Hz, =$CHCH_2$), 1.61 (m, 2 H, $(H_3C)CH(OH)CH_2$), 1.16, (d, 3 H, J = 8 Hz, CH_3); mass spectrum, m/e 183 ($M^{+\cdot}$), 165 (M^+ − H_2O), 146. Anal. Calcd for $C_9H_{13}NO_3$: C, 58.99; H, 7.17; N, 7.65. Found: C, 59.17; H, 7.16; N, 7.37. A subsequent repeat experiment and chromatography gave **29b** (68%) and the *Z* isomer **30** (8%): IR (CH_2Cl_2) 3600, 3400, 2920,

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1775, 1728, 1670, 1130 cm^{-1}. ^1H NMR ($(CD_3)_2CO$) δ 7.5 (br s, 1 H), 5.95 (tt, 1 H, J = 8, 2 Hz), 3.8 (br q, 2 H, J = 8 Hz), 3.2 (br s, 2 H), 2.5 (br q, 2 H, J = 8 Hz), 1.4 (m, 2 H), 1.1 (d, 3 H, J = 8 Hz).

3(*S*(*R*))-[5(*R*(*S*))-Methyl-2(*S*(*R*))-tetrahydrofuryl]-3-(phenylselenenyl)-2,5-pyrrolidinedione (31) and the Cis Isomer 32. The unsaturated hydroxy imide **29b** (100 mg) was dissolved in MeCN (4 mL) and stirred while PhSeCl (115 mg) was added in five portions. The mixture was stirred at room temperature for 48 h and then treated with a further portion of PhSeCl (11.5 mg). After stirring a further 18 h, TLC analysis ($CHCl_3$ on silica gel) indicated that the reaction was complete; the volatile material was evaporated and the crude yellow oil flash chromatographed ($CHCl_3$ to $CHCl_3$–MeOH, 9:1) to give (in order of elution) the two isomeric selenides **32** (9.2 mg, 5%) and **31** (147 mg, 80%) as white solids. Recrystallization from EtOAc–pentane gave **31** as white crystals: mp 107–110 °C; IR (CH_2Cl_2) 3380, 1780, 1720, 1332, 1171, 1073, 970 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.93 (br s, 1 H, NH), 7.62 (m, 2 H), 7.33 (m, 3 H), 4.55 (dd, 1 H, J = 6.3, 9.6 Hz, —(PhSe)CC*H*O—), 4.18 (m, 1 H, $(CH_3)C\mathit{H}O$), 3.10 (d, 1 H, J = 18.5 Hz, O=CCH_2^{α}), 2.65 (d, 1 H, J = 18.5 Hz, O=CCH_2^{β}), 2.29 (m, 1 H, —C(SePh)CHCH_2^{β}), 2.10 (m, 1 H, —C(SePh)CHCH_2^{α}), 1.75 (m, 1 H, H_3CCHCH_2), 1.56 (m, 1 H, $H_3CCHCH_2^{\alpha}$), 1.19 (d, 3 H, J = 5.9 Hz, CH_3); mass spectrum, m/e 339 ($M^{+\cdot}$), 255 ($M^+ - C_5H_8O$), 85 (C_5H_9O). Anal. Calcd for $C_{15}H_{17}NO_3Se$: C, 53.25; H, 5.08; N, 4.14. Found: 53.35; H, 5.22; N, 4.09.

Recrystallization of crude **32** from EtOAc–pentane gave **32** as white microcrystals: mp 130–132 °C; IR (CH_2Cl_2) 3460, 3385, 1722, 1335, 1170, 1074 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.6 (br s, 1 H, NH), 7.64 (m, 2 H), 7.33 (m, 3 H), 1.35 (t, 1 H, J = 7.6 Hz, —C(SePh)C*H*O—), 4.05 (m, 1 H, $(H_3C)C\mathit{H}O$), 3.77 (d, 1 H, J = 18.5 Hz, O=CCH_2^{α}), 2.64 (d, 1 H, J = 18.5 Hz, O=CCH_2^{β}), 2.13 (m, 2 H, —C(SePh)CHCH_2), 1.80 (m, 1 H, $H_3CCHCH_2^{\beta}$), 1.48 (m, 1 H, $H_3CCHCH_2^{\alpha}$), 1.15 (d, 3 H, J = 5.9 Hz, CH_3); mass spectrum, m/e 339 ($M^{+\cdot}$), 255 ($M^+ - C_5H_8O$), 85 (C_5H_9O). Anal. Calcd for $C_{15}H_{17}NO_3 \cdot {}^1/_2H_2O$: C, 51.87; H, 5.37; N, 3.93. Found; C, 51.50; H, 4.97; N, 3.99.

3(*S*(*R*))-(Phenylselenenyl)-[2(*S*(*R*))-tetrahydrofuryl]-2,5-pyrrolidinedione (33). A stirred solution of the unsaturated hydroxy imide **29a** (17 mg) in MeCN (1 mL) was treated with PhSeCl (20.1 mg) in one portion at room temperature. Stirring was continued for 44 h, at which time TLC analysis ($CHCl_3$–MeOH, 9:1) indicated complete reaction. Evaporation of the solvent and flash chromatography (silica gel, $CHCl_3$) gave the desired selenide **33** as a colorless glass (30 mg, 93%): IR (Nujol) 3420, 3190, 1775, 1718, 1340, 1190, 1055, 800, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (br s, 1 H, NH), 7.5 (m, 5 H), 4.3 (t, 1 H, J = 7 Hz, —CHO—), 3.8 (t, 2 H, J = 8 Hz, —CH_2O), 3.1 (d, 1 H, J = 18 Hz, O=CCH_2^{α}), 2.6 (d, 1 H, J = 18 Hz, O=CCH_2^{β}), 1.6–2.4 (m, 4 H); mass spectrum, m/e 325 ($M^{+\cdot}$), 245 ($M^+ - C_4H_6O$), 157 ($PhSeH^+$); exact mass calcd for $C_{14}H_{15}NO_3Se$ ($M^{+\cdot}$) 325.0217, found ($M^{+\cdot}$) 325.0224.

3-[5(*R*(*S*))-Methyl-2(*S*(*R*))-tetrahydrofuryl]-1*H*-pyrrole-2,5-dione (34b). Method A: By Hydrogen Peroxide Oxidation. A stirred solution of the succinimide derivative (**31**) (100 mg) in tetrahydrofuran (3.5 mL) at 0 °C was treated dropwise with a solution of H_2O_2 in H_2O (30% w/v; 350 μL). The mixture was treated with HOAc (50 μL) and stirred a further 40 min. Aqueous $NaHCO_3$ solution (saturated, 1 mL) was added, the mixture was allowed to attain room temperature and extracted with Et_2O (5 × 10 mL). Drying, evaporation, and flash chromatography (silica gel, $CHCl_3$ to $CHCl_3$–MeOH, 9:1) gave the desired maleimide **34b** (53 mg, 99%) as a colorless glass: IR (CH_2Cl_2) 3520, 3420, 2910, 1770, 1718, 1630, 1335, 1067, 1020, 928, 870 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.55 (br s, 1 H, NH), 6.47 (br s, 1 H, HC=), 4.91 (dt, 1 H, J = 1.3, 7.3 Hz, =CCHO—), 4.26 (dq, 1 H, J = 5.9, 13.5 Hz, $H_3CC\mathit{H}O$), 2.47 (m, 1 H, =CCHCH_2^{β}), 2.10 (m, 1 H, =CCHCH_2^{α}), 1.85 (m, 1 H, $H_3CHCH_2^{\beta}$), 1.60 (m, 1 H, $H_3CHCH_2^{\alpha}$), 1.26 (d, 3 H, J = 5.9 Hz, H_3C); mass spectrum, m/e 181 ($M^{+\cdot}$), 165 ($M^+ - NH_2$), 124 (base peak). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12. Found: C, 59.88; H, 6.39.

Method B: By Ozonolysis. A solution of the succinimide derivative **31** (500 mg) in dry CH_2Cl_2 (5 mL) was cooled to −78 °C. O_3 was bubbled through the mixture until a light blue coloration was observed, and the solution was purged successively with O_2 and Ar, treated with 1 drop of Et_3N, and warmed to 40 °C in a water bath. The bright yellow solution was evaporated to dryness and the residue chromatographed on silica ($CHCl_3$ to $CHCl_3$–MeOH, 9:1) to give the desired maleimide derivative **34b** (258 mg, 95%) as a light yellow glass spectroscopically identical with that prepared by method A above.

3-(2-Tetrahydrofuryl)-1*H*-pyrrole-2,5-dione (34a). A solution of the succinimide derivative **33** (28 mg) in CH_2Cl_2 (10 mL) was cooled to −78 °C and treated with O_3 until a pale blue color persisted (ca. 45 min). The mixture was purged with O_2 and with Ar and allowed to warm to room temperature. The yellow solution was dried and evaporated and the resulting yellow gum chromatographed (SiO_2–$CHCl_3$) to give the desired maleimide derivative **34a** (12 mg, quantitative) as a white solid: mp 102–104 °C (EtOAc–pentane); IR (CH_2Cl_2) 3430, 2940, 2880, 1775, 1720, 1630, 1600, 1510, 1438, 1169, 1119, 1087, 1067, 1022, 915, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (br s, 1 H, NH), 6.16 (t, 1 H, J = 1.5 Hz, HC=C), 4.5 (dt, 1 H, J = 1.5, 7 Hz, =CCHO—), 3.66 (m, 2 H, H_2CO—), 1.3–2.3 (m, 4 H); mass spectrum, m/e 167 ($M^{+\cdot}$), 139 ($M^{+\cdot}$), 139 ($M^+ - CO$), 124 ($M^+ - NHCO$), 111 ($M^+ - HCCONH$); exact mass calcd for $C_8H_9NO_3$ ($M^{+\cdot}$) 167.0582, found ($M^{+\cdot}$) 167.0576.

3(*E*)-(2(*S*),3(*S*),4(*R*),5-Tetrahydroxy-1-pentylidene)-2,5-pyrrolidinedione (35). To a stirred suspension of the ylide **8a** (21.54 g) in dry THF (150 mL) was aded, in a single portion, solid D-ribose **2** (4.5 g). The mixture was heated under reflux for 192 h while the reaction was monitored by TLC analysis (silica gel, $CHCl_3$–MeOH, 9:1, or EtOAc–AcMe–MeOH, 15:4:1, or optimally, C_{18} reverse-phase silica plates, H_2O). The solvent was evaporated and the crude product partitioned between H_2O (150 mL) and CH_2Cl_2 (150 mL). The aqueous phase was evaporated at reduced pressure to low volume and chromatographed on C_{18} reverse-phase silica gel (100:1 w/w) using water as eluant. The rapidly eluted product was isolated by evaporation of the water, rechromatography on silica gel (EtOAc to EtOAc–AcMe–MeOH, 15:4:1, gradient the proportion of AcMe to MeOH always being 4:1) and recrystallization from EtOH–EtOAc to give the desired compound **35** (5.2 g, 75%) as white crystals: mp 134–136 °C; $[\alpha]^{20}_D$ −2.4° (c 1.0, H_2O); UV λ_{max} (H_2O) 222 nm (ϵ 7870); IR (Nujol) 3580, 3440, 2920, 2860, 1750, 1700, 1670, 1300, 1250, 1204, 1072, 1029, 1010 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 6.74 (dt, 1 H, J = 8.3, 2.4 Hz), 4.65 (s, HOD) partially obscuring 4.58 (dd, J = 4.15, 8.3 Hz), 3.7–3.9 (m, 2 H), 3.58–3.7 (m, 2 H), 2.51 (d, 2 H, J = 2.4 Hz); ^{13}C NMR (noise decoupled, D_2O) δ 33.17, 62.69, 69.66, 71.74, 73.56, 129.69, 134.33, 134.63, 172.99 (relative to 1,4-dioxane = 66.50 as internal standard); mass spectrum, m/e 232 ($M^+ + 1$), 213 ($M^+ - H_2O$), 195 ($M^+ - 2H_2O$). Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.63; N, 6.06. Found: C, 46.60; H, 5.63; N, 5.90.

Preparation of Showdomycin (1) and 1′-*epi*-Showdomycin (36). A stirred suspension of **35** (231 mg) in MeCN (14 mL) was heated to 65 °C and treated with PhSeCl (200 mg). The reaction was stirred at 65 °C for 29 h and followed on TLC (EtOAc–AcMe–MeOH, 15:4:1). The mixture was allowed to reach ambient temperature, treated with aqueous H_2O_2 solution (10 vol, 5 mL), and stirred until all selenium-containing material (TLC, EtOAc–AcMe–MeOH, 15:4:1, spray 0.1% $PdCl_2$ in 0.1 M HCl) was consumed. Volatile materials were evaporated at reduced pressure and the residue chromatographed (silica gel, EtOAc–EtOH, 19:1) to give a mixture of **1** and **36** in 80% crude yield. HPLC (Zorbax ODS 9-mm column, water, 3 mL/min, UV detection at 254 nm) allowed separation of the products. Recrystallization of the faster running fraction (retention time 18.5 min) from EtOAc–pentane gave **36** as white crystals (95 mg, 41%): mp 139–140 °C (lit.[28] mp 139–40 °C); $[\alpha]_D$ −76° (c 0.1, H_2O), (lit.[28] $[\alpha]_D$ −77°); IR (KBr) 3562, 3412, 3340, 2925, 1770, 1708, 1685, 1638, 1392, 1320, 1103, 1088, 1047, 640 cm^{-1}; ^1H NMR (270 MHz, $(CD_3)_2CO$) δ 9.70 (br s, 1 H, NH), 6.45 (d, 1 H, J = 2 Hz, H-4), 4.91 (dd, 1 H, J = 2.4 Hz, H-1′), 4.1–4.4 (m, 4 H, 3 × OH and H-5′), 3.70–3.95 (m, 3 H, H-5′, H-3′, H-2′), 3.78 (m, 1 H, H-4′). The material was identical (mmp) with an authentic sample of **36**. Recrystallization of the slower running fraction (retention time 20.0 min) from the same system gave **1** as white crystals (27 mg, 13%): mp 159–160 °C (lit.[28] mp 160–161 °C); $[\alpha]_D$ +51° (c 0.1, H_2O), (lit.[28] $[\alpha]_D$ +49.9°); IR (KBr) 3464, 3404, 3216, 1772, 1705, 1643, 1447, 1399, 1264, 1233, 1112, 1025, 1004, 985, 966, 799, 770 cm^{-1}; ^1H NMR (270 MHz, $(CD_3)_2CO$) δ 9.80 (br s, 1 H, NH), 6.71, (d, 1 H, J = 2 Hz, H-4),

4.70 (dd, 1 H, J = 1.4, 4.4 Hz, H-1′), 4.48 (br s, 1 H, OH), 4.13 (m, 3 H, H-2′, H-3′, OH), 3.93 (m, 2 H, H-4′, OH), 3.55–3.75 (AB m, 2 H, H-5′). This material was identical in all respects with an authentic sample of 1.

3(*E*)-[[5(*S*)-(1(*R*),2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4(*S*)-yl]methylene]-2,5-pyrrolidinedione (44a). To a stirred suspension of the ylide **8a** (8.98 g) (prepared in situ from maleimide and triphenylphosphine) in 1,2-dimethoxyethane (10 mL) was added a solution of 2,3-*O*-isopropylidene-D-ribofuranose **37b** (960 mg) in the same solvent (5 mL). The mixture was heated to 60 °C and stirred at that temperature for 290 h. The volatile materials were evaporated and the residue was subjected to chromatography (silica gel, $CHCl_3$ to $CHCl_3$–MeOH, 15:1, gradient) to give **44a** as a clear gum. Crystallization from EtOAc or EtOAc–pentane gave the desired unsaturated imide **44a** (705 mg, 52%) as white crystals: mp 137–139 °C dec; $[\alpha]_C$ −4.5° (c 0.1, EtOH); UV (EtOH) λ_{max} 243 nm (log ϵ = 3.63); IR (CH_2Cl_2) 3490, 3400, 1778, 1732 (Nujol) 3490, 3160, 3070, 1760, 1720, 1685, 1350, 1250, 1210, 1162, 1060, 860, 840 cm^{-1}; ^{1}H NMR (270 MHz, $(CD_3)_2CO$) δ 10.13 (br s, 1 H), 6.64 (dt, 1 H, J = 8.0, 2.5 Hz), 4.88 (br t, 1 H, J = 7.4 Hz), 4.05–4.30 (m, 2 H), 3.70 (m, 2 H, CH_2OH) 3.53 (m, 1 H, CHOH), 2.85 (m, 1 H, OH), 1.45 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3); mass spectrum, m/e 272 (M^+ + 1), 256 (M^+ − Me), 238 (M^+ − Me − H_2O), 214 (M^+ − C_3H_5O), 196 (M^+ − C_3H_5O − H_2O), 181 (M^+ − $C_3H_6O_3$). Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.14; H, 6.27. Found: C, 53.22; H, 6.40.

1-(Triphenylmethyl)-3-(triphenylphosphoranylidene)-2,5-pyrrolidinedione (8b). A stirred solution of *N*-tritylmaleimide (1.7 g) in CH_2Cl_2 (15 mL) was treated dropwise with a solution of Ph_3P (1.31 g) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature overnight, evaporated to dryness, and recrystallized from EtOAc–pentane to give the ylide **8b** (3.0 g, 100%) as light yellow crystals: mp 162–165 °C; UV ($CHCl_3$) λ_{max} 258 nm (log ϵ = 3.85), 305 nm (log ϵ = 3.45); IR (CH_2Cl_2) 1708, 1638, 1330, 1100 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.0–7.7 (m, 30 H), 2.9 (br s, 2 H). This material was further characterized as its derivative with formaldehyde 3-methylene-1-(triphenylmethyl)-2,5-pyrrolidinedione: mp 200 °C; IR 2926, 1782, 1715, 1670, 1324, 1128, 825 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.8–7.4 (m, 15 H), 6.06 (m, 1 H, =CH_2 syn to carbonyl), 5.27 (m, 1 H, =CH_2 anti to carbonyl), 3.06 (m, 2 H, O=CCH_2). Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.59; H, 5.38; N, 3.97. Found: C, 81.45; H, 5.32; N, 3.90.

3(*E*)-[[5(*S*)-(1(*R*),2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4(*S*)-yl]methylene]-1-(triphenylmethyl)-2,5-pyrrolidinedione (44b) and the *Z* Isomer 45. A stirred solution of *N*-tritylmaleimide (1.7 g) in CH_2Cl_2 (15 mL) was treated dropwise with a solution of Ph_3P (1.31 g) in CH_2Cl_2 (10 mL) and stirred overnight at room temperature. A solution of 2,3-*O*-isopropylidene-D-ribofuranose **37b** (0.48 g) in CH_2Cl_2 (5 mL) was then added and the mixture was stirred 240 h while the reaction was monitored by TLC ($CHCl_3$–MeOH, 19:1). Evaporation of the mixture and chromatography (SiO_2, 70 g with $CHCl_3$ to $CHCl_3$–MeOH, 19:1, eluant gradient) gave the desired products as pale yellow solid foams: **44b** (100 mg), **45** (72 mg), and a mixed fraction (**44b**:**45** = 7:3) (219 mg) (total yield 391 mg, 30%) and recovered **37b** (326 mg, 68%). The products were characterised as follows. **44b**: IR (CH_2Cl_2) 3560, 3410, 2880, 1770, 1700, 1620, 1320, 1160, 1060, 890 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.0–7.7 (m, 15 H), 6.62 (br d, 1 H, J = 7.9 Hz, H-1′), 4.66 (br t, 1 H, J = ca. 7.9 Hz, H-2′), 4.00 (dd, 1 H, J = 5.9, 9.2 Hz, H-5′), 3.4–3.7 (m, 5 H), 3.34 (br d, 1 H, J = 21.7 Hz, O=CCH_2^a), 3.15 (br d, 1 H, J = 21.7 Hz, O=CCH_2^b), 1.35 (s, 3 H), 1.22 (s, 3 H); mass spectrum, m/e 513 ($M^{+\cdot}$), 259, 243 (base peak), 182, 165; exact mass calcd for $C_{31}H_{31}NO_6$ ($M^{+\cdot}$) 513.2151, found ($M^{+\cdot}$) 513.2158. **45**: IR (CH_2Cl_2) 3560, 3460, 2880, 1770, 1700, 1635 (shoulder), 1320, 1120, 1062, 900, 880 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.0–7.6 (m, 15 H), 6.0 (br d, 1 H, J = 8.6 Hz), 5.74 (br t, 1 H, J = 8.6 Hz), 4.08 (dd, 1 H, J = 6.6, 7.9 Hz), 3.3–4.7 (m, 5 H), 3.23 (d, 1 H, J = 21 Hz), 3.12 (d, 1 H, J = 21 Hz), 1.38 (s, 3 H), 1.23 (s, 3 H); mass spectrum, m/e 513 ($M^{+\cdot}$), 259, 243 (base peak), 182, 165. Anal. Calcd for $C_{31}H_{31}NO_6 \cdot 2H_2O$: C, 67.76; H, 6.38; N, 2.55. Found: C, 67.56; H, 6.05; N, 2.29.

3,3-Dimethyl-6(*R*)-(2,5-dioxo-3-(phenylselenenyl)-1-(triphenylmethyl)-3-pyrrolidinyl)-8(*R*)-(hydroxymethyl)-(1-(*R*),5(*R*))-2,4,7-trioxabicyclo[3.3.0]octane (46). A stirred solution of **44b** and **45** (839 mg) in dry CH_2Cl_2 (37 mL) was treated with finely ground K_2CO_3 (1.27 g) at −78 °C. Vigorous stirring was maintained while PhSeCl (374.7 mg) was added in three portions. After a period of 1 h the mixture was allowed to warm to room temperature and stirred for 48 h during which the reaction was monitored by TLC ($CHCl_3$–MeOH, 9:1; detection UV, 0.1% $PdCl_2$ in 0.1 M HCl and 10% H_2SO_4 in ethanol sprays). Ultrasonication for 5 h and stirring for a further 10 h followed by recooling to −78 °C and treatment with further portions of K_2CO_3 (1.27 g) and PhSeCl (374.7 mg). The mixture was held at −78 °C for 1 h, warmed to room temperature, stirred vigorously for 15 h, and subjected to ultrasonication for 3 h. The mixture was then treated with saturated aqueous $NaHCO_3$ (40 mL) and the organic layer washed successively with a further portion of saturated aqueous $NaHCO_3$ (40 mL) and with brine (40 mL). Drying and evaporation of the organic phase followed by flash chromatography (CH_2Cl_2 as eluant) gave **46** (187 mg, 17%) as a colorless glass: IR (CH_2Cl_2) 3580, 2900, 1770, 1705, 1320, 1200, 1150, 1070, 1045, 855 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.1–7.8 (m, 20 H), 5.20 (dd, 1 H, J = 4.3, 6.9 Hz), 4.39 (dd, 1 H, J = 5.3, 6.9 Hz), 4.15 (d, 1 H, J = 4.3 Hz), 3.85 (m, 1 H, H-4′), 3.46 (dd, 1 H, J = 3.3, 12.2 Hz), 3.0–3.4 (br s, 1 H, OH), 3.25 (dd, 1 H, J = 5.6, 12.2 Hz), 2.98 (d, 1 H, J = 18.5 Hz), 2.72 (d, 1 H, J = 18.5 Hz), 1.53 (s, 3 H), 1.26 (s, 3 H); mass spectrum, m/e 669 ($M^{+\cdot}$), 592 (M^+ − Ph), 553 (M^+ − Se − 2H_2O), 512 (M^+ − SePh), 427 (M^+ − CPh_3); exact mass calcd for $C_{37}H_{35}NO_6Se$ ($M^{+\cdot}$) 669.1630, found ($M^{+\cdot}$) 669.1610. Other products isolated from this experiment included the starting materials **44b** and **45** (497 mg, 60% recovery) and a minor byproduct (18 mg) which was not identified.

2,3-*O*-Isopropylidene-*N*-(triphenylmethyl)showdomycin (47). A stirred solution of the selenide **46** (109 mg) in THF (5 mL) containing HOAc (1 drop) was treated dropwise at 0 °C with aqueous H_2O_2 (100 vol, 117 μL). The mixture was stirred for 40 min at this temperature, treated with saturated aqueous $NaHCO_3$ (2 mL), and allowed to warm to room temperature. Extraction of the products with Et_2O (4 × 15 mL) and washing of the combined extracts with saturated aqueous $NaHCO_3$ (5 mL) and brine (2 × 5 mL) gave, after drying and evaporation of the solvent, a colorless glass which was chromatographed ($CHCl_3$) and recrystallized from EtOAc–pentane to give the desired showdomycin derivative **47** (62.0 mg, 76%) as white crystals: mp 167–170 °C; UV (EtOH) λ_{max} 220 nm (log ϵ = 4.12), 233 (4.11), 331 (2.98); IR (CH_2Cl_2) 3660, 3590, 3480, 2900, 1758 (shoulder), 1708, 1600, 1335, 1080, 853 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.1–7.5 (m, 15 H), 6.49 (d, 1 H, J = 0.9 Hz, H-4), 4.76 (m, 2 H, H-1′ and H-3′), 4.65 (br t, 1 H, J = 6 Hz, H-2′), 4.22 (m, 1 H, H-4′), 3.77 (dd, 1 H, J = 2.6, 12.3 Hz, H-5′^{a}), 3.62 (dd, 1 H, J = 3.4, 12.3 Hz, H-5′^{b}), 2.04 (br s, 1 H, OH), 1.55 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3); mass spectrum, m/e 511 ($M^{+\cdot}$), 243 (CPh_3^+), 228 (showdomycin − 1), 165 (CPh_3^+ − PhH). Anal. Calcd for $C_{31}H_{29}NO_6 \cdot {}^1/_2H_2O$; C, 71.54; H, 5.77; N, 2.69. Found: C, 71.51; H, 5.80; N, 2.56.

Deprotection of 1-(Triphenylmethyl)-1*H*-pyrrole-2,5-dione. *N*-Tritylmaleimide (100 mg) was dissolved in dry CF_3CO_2H (5 mL) and treated with H_2O (1 drop). The mixture was stirred 5 days, treated with silica (100 mg), and evaporated to a pale yellow powder. This was applied dry to the top of a column of silica gel (1 g) and chromatography was effected with a $CHCl_3$ to $CHCl_3$–MeOH, 9:1, eluant gradient. Maleimide was obtained in good yield (19 mg, 65%). No tritylmaleimide was recovered.

Preparation of Showdomycin (1) by Deprotection of 47. A stirred solution of **47** (10.2 mg) in CF_3CO_2H (5 mL) was treated with H_2O (1 drop) and stirred 5 days at room temperature. Silica gel (10 mg) was added and the solvent evaporated. The resulting powder was poured on top of a column of silica gel (100 mg) and the products were eluted with a pentane to EtOAc–MeOH, 9:1, gradient. Showdomycin (4 mg) was isolated and was found to be identical (NMR, IR, mp) with material previously synthesized.

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A Direct Synthesis of Trichodiene

George A. Kraus* and P. J. Thomas

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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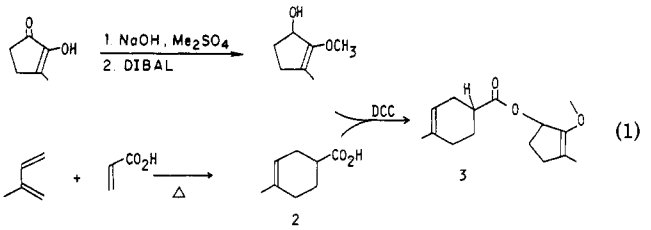
The synthesis of trichodiene via the Ireland modification of the Claisen rearrangement is described. The enol ether resulting from the rearrangement functions as a protecting group during two reduction steps. The enol ether diastereomers can be conveniently separated by flash chromatography.

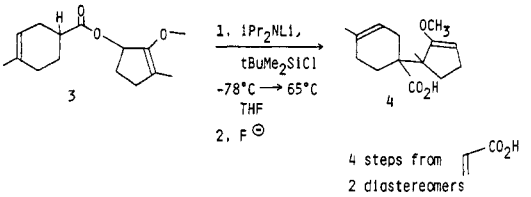
The trichothecene sesquiterpenes pose a fascinating challenge to synthetic organic chemists. With two adjacent quaternary centers plus an array of stereogenic carbon atoms of various oxidation states, complex trichothecenes such as deoxynivalenol and T-2 toxin have not been synthesized.[1] Less complex compounds such as verrucarol,[2] anguidin,[3] and calonectrin[4] have been prepared. The biogenetic precursor to all of the aforementioned compounds is trichodiene **1**. Because of its comparative simplicity and its pivotal role in trichothecene production in nature, several syntheses of trichodiene have been developed.[5-10] Recent syntheses have featured a nonstereospecific Claisen rearrangement,[6] a Nazarov cyclization/fragmentation strategy,[7] and a clever Diels–Alder-based approach.[8] In the context of developing a practical route to the complex trichothecenes, we recently employed the Ireland modification of the Claisen rearrangement[11] and now report a direct synthesis of **1**.

The synthesis starts with the commercially available 3-methylcyclopentane-1,2-dione (eq 1). Formation of the



(1)

enol ether with dimethyl sulfate and sodium hydroxide[12] followed by reduction of the ketone with diisobutylaluminum hydride provided an unstable allylic alcohol which was converted into a mixture of diastereomeric esters **3** with acid **2**[13] and dicyclohexylcarbodiimide.[14] Ester **3** was transformed into the *tert*-butyldimethylsilyl ester of **4** by deprotonation with lithium diisopropylamide (LDA), silylation with *tert*-butyldimethylchlorosilane, and then heating in refluxing THF to effect the Claisen rearrangement (eq 2). This rearrangement afforded two



(2)

products in essentially equal amounts. The lack of selectivity was expected and reflects the absence of steric or electronic direction in the formation of the ketene acetal.[15] Surprisingly, treatment of the silyl ester with lithium aluminum hydride resulted in desilylation rather than reduction. This must be a consequence of the highly crowded environment around the ester. Desilylation with tetrabutylammonium fluoride was more convenient and generated acid **4** in quantitative yield. Esterification with diazomethane followed by reduction of the ester with lithium aluminum hydride produced an unstable alcohol. This alcohol in the presence of even traces of acid formed an internal ketal by reaction with the enol ether. We solved this problem by forming the mesylate with methanesulfonyl chloride and triethylamine immediately after reduction.[16] The tosylate was also prepared. However, its formation was accompanied by significant amounts of the undesired internal ketal product (eq 3). Reduction of the mesylate was best accomplished with a zinc–copper couple and excess sodium iodide in dimethoxyethane with an equal volume of hexamethylphosphoric triamide.[17] The two enol ethers were distinct spots on TLC in pentane and

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