J. Org. Chem. **1988**, *53*, 1461-1466

(+)-Pleuromutilin Synthetic Studies. Examples of Intramolecular Hydrogen Abstraction by the β-Carbon of a 2-Cyclopentenone Subunit with Resultant α-Coupling

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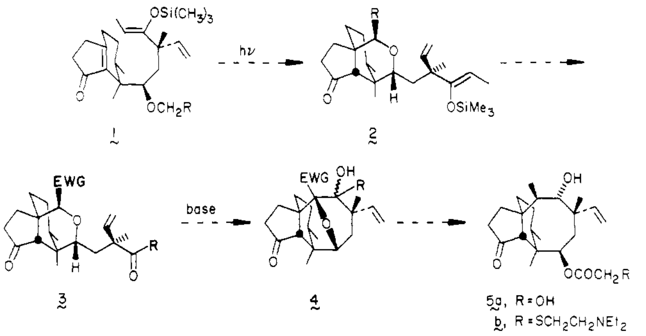
Received August 17, 1987

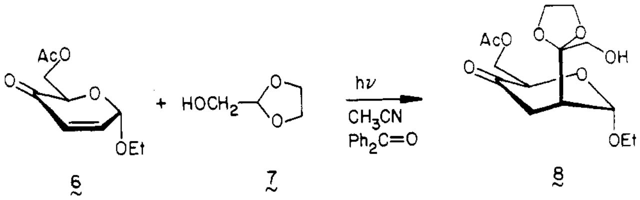
Two bicyclic enones carrying an ether side chain (19 and 22) were irradiated in order to effect photocyclization. Of the several possible pathways available to these molecules, the only process followed is that involving abstraction by the β-carbon of the cyclopentenone subunit of a CH_2O hydrogen and intramolecular coupling of the resulting biradical. The closely similar spectra of 21 and 24 suggested that they are structurally related. The regio- and stereochemical disposition of the lactone ring in the latter was established chemically (conversion to lactone 29 followed by base-promoted cleavage) and crystallographically (diffraction study of 34). The course of these excited-state reactions was not that predicted on the basis of ground-state steric and conformational factors. MM2 calculations indicate the cyclizations not to be thermodynamically driven. The kinetic control probably stems from conformational features adopted by the photoexcited molecules which open the door for preferred formation of the indicated biradical.

The preceding articles[3,4] contain two major points of emphasis: (a) the eight-membered ring common to pleuromutilin (**5a**) and tiamulin (**5b**) can be regiospecifically cleaved to give highly functionalized bicyclic enones, which have in turn been prepared de novo in optically active condition, and (b) reconstruction of the cyclooctane ring is hampered by steric and entropic factors. The basis of our original plan for return to the natural products in an effective relay synthesis was appropriate photocyclization of several available ketones such as **1** to **2**. Replacement of R in **2** by an electron-withdrawing group (EWG) and conversion of the silyl enol ether functionality to an electrophilic center as in **3** was to precede C–C bond formation via a six-centered transition state. A short series of conventional steps was ultimately to deliver the targets **5**.



The presumed effectiveness of this approach was considered to be the manner in which direct construction of the eight-membered ring was skirted. Furthermore, the ring closure anticipated to be the more difficult was to be accomplished photochemically. For this to be a viable approach, however, it was first necessary to determine the feasibility of the excited-state process and to demonstrate that the several controlling elements at play in this step do proceed with formation of the desired tetrahydropyran ring.

The Photochemical Precedence. In recent years, the capacity of cyclic enones for *intermolecular* photosensitized (benzophenone) conjugate addition–alkylation in the presence of alcohols[5,6] has been extensively developed for synthetic applications.[7] The resulting γ-keto alcohols such as **8** are formed in high yield and often, as in this example, with complete stereoselectivity.



Formally analogous *intramolecular* variants of this process are known. The sensitized conversion of taxinine (**9**) and its derivatives into isomers of type **10** has been reported.[8] These and related triplet-state photoisomerizations,[9-12] e.g. **11** → **12**,[13] are viewed as proceeding via intramolecular hydrogen transfer to the α-carbon of the enone double bond, and involving biradical intermediates.

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[1] National Science Foundation Predoctoral Fellow, 1981–1984.

[2] Author to whom inquiries concerning the X-ray analysis should be directed.

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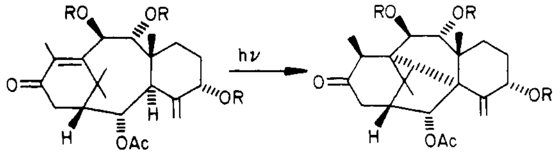
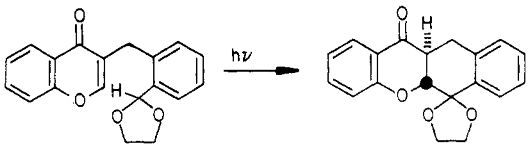
Table I. Photochemical Reaction Conditions Employed for Attempted Cyclization of 19

lamp source	filter	solvent	time, h	result
2537 Å (Rayonet reactor)		MeOH	5	dec
		hexane	10	dec
3500 Å (Rayonet reactor)		hexane	10	dec
450-W Hanovia lamp	Pyrex	C_6H_6	5	dec
	Pyrex	MeOH	1	dec
	Pyrex	hexane	30	polymzatn
	Pyrex	$(CH_3)_2CO/C_6H_6$	14	dec
	Corex	C_6H_6	16	dec
	Corex	Et_2O	6	no reactn
	Vycor	$(CH_3)_2CO$	4	dec
	uranium glass	cyclohexane	72	no reactn
	Pyrex	CH_2Cl_2	2–15	21 formed

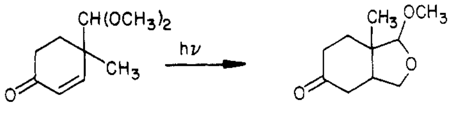
In contrast, the transformation of **13** into **14** apparently occurs neither from the lowest $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ triplet states nor from the first singlet $n \rightarrow \pi^*$ state but rather from the reactive second singlet $\pi \rightarrow \pi^*$ state.[10c,d]



9 **10**

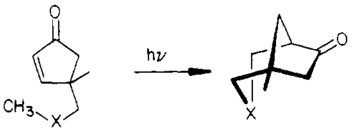


11 **12**



13 **14**

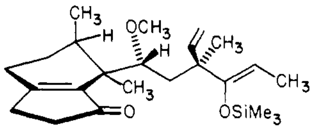
α,β-Unsaturated ketones are also capable of intramolecular hydrogen abstraction by the β-carbon atom.[14,15] In-depth investigations in selected cases have established that formation of the biradical pair proceeds uniformly from a readily accessible triplet state. Agosta has noted that the efficiency for conversion of **15** into **16** is doubled when X is altered from CH_2 (11%) to O (20%).[14a]



15a, X=CH2 **16a**, X=CH2
b, X=O **b**, X=O

Cases are known in which abstraction by both centers occurs in a single molecule.[14b,16] Generally, however, steric and/or entropic factors combine to favor transfer to one site or the other. Substrates **15a** and **15b**, for example, are so constructed that the abstractable hydrogen is positioned in a highly favorable[17] 1,5-relationship to the β-carbon. In the taxinine system **9**, the polycyclic structure holds the transferable hydrogen rather close to the π-lobe of the α-carbon atom in the ground state.

In **1**, there exists a good likelihood that the dominant conformation projects the large side chain in the equatorial direction as in **17**. No intramolecular photochemistry is likely to operate when this geometry is adopted because distances between reactive centers are too great. Flexing of the six-membered ring leads to **18**, a conformation where at least one of the methyl hydrogens α to ether oxygen can become aligned so as to achieve good overlap with the enone double bond. Molecular models suggested there to be reasonable geometric differences between abstraction by the α- and β-carbons, with the 1,5-relationship to the α-site appearing especially favorable as in **13**.



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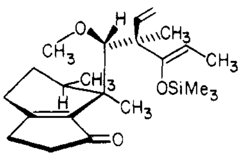

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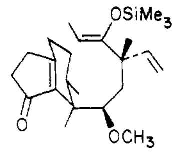
The key question, therefore, was whether photolysis of **1** would follow precedent, result in ready abstraction by the α-carbon of a proximate CH_2O hydrogen atom, and ultimately give rise to **2**. In this analysis, account has not been taken of the potentially important role that may exist for other factors such as the availability of competing processes and the relative stability of intermediate species. These options could in principle curtail abstraction completely or lead to products arising from abstraction by the β-carbon atom.

Photochemical Cyclizations. We first examined the photolysis of **19** in a variety of solvents with different lamp sources and filters (Table I). For the most part, either no reaction was observed or decomposition/polymerization ensued. However, the conditions reported by Cargill[18] did prove efficacious. Irradiation of dilute methylene chloride solutions of **19** with a 450-W Hanovia lamp through Pyrex for 4–6 h resulted in formation of a single oily photoisomer in 53% yield. The spectral data for this product indicated



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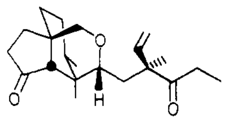

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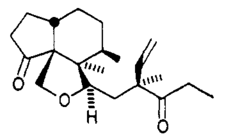

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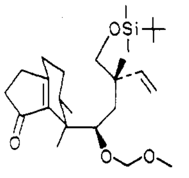
that the enone and methoxyl functionalities were no longer present. The ^1H signals of the vinyl group remained clearly defined well downfield of the new AB pattern at δ 3.82 and 3.66 (in $CDCl_3$) characteristic of a methylene group in an oxygen heterocycle. Detailed NMR studies showed the photoproduct to possess a structure compatible with **20** or **21**, but no firm distinction could be made between these isomers. At this juncture, it was considered advisable to move ahead and examine the excited-state chemistry of **22**. In this particular example, the potential existed for definitive proof of photoproduct structure by chemical methods. Following considerable experimentation, **22** was found to respond most favorably to irradiation in a Rayonet reactor when dissolved in methylene chloride containing acetone. Under these circumstances, a pair of readily separable diastereomeric products (**23a**/**23b** or **24a**/**24b**) was obtained in 54% and 9% yields (respectively).



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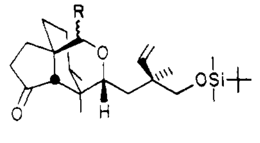
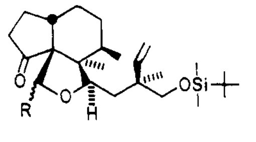
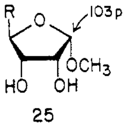


23a, R = β-OCH_3
b, R = α-OCH_3



24a, R = β-OCH_3
b, R = α-OCH_3

As in the case of **20** and **21**, the assignment of absolute stereochemistry α to the carbonyl group was viewed as solidly founded upon the conformational considerations developed in **17** and **18**. Epimerization in **20** and **23** would obviously introduce excessive strain into these molecules. The configuration at the original β-carbon should also be as indicated, since bonding only from that face syn to the methoxyl or MOM substituents is sterically allowed. The stereochemical status of the anomeric centers was deduced on the basis of ^1H and ^{13}C chemical shift data. It is widely recognized that an equatorial proton adjacent to a polar group such as methoxyl is downfield shifted relative to the corresponding axial proton in the epimer.[19] The major and minor photoproducts of **22** exhibit their anomeric protons at δ 4.86 and 4.76, respectively. Analogy for representative ^{13}C values may be drawn from the furanosides **25** and **26**.[20] The shielding associated with **23a** or **24a**



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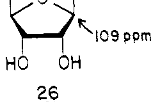

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(108.0 ppm) is considerably less than that found in the **b** series (99.5 ppm). The consistency of these data was considered confirmatory for the presence of an axial methoxyl group in the more dominant cyclic acetal.

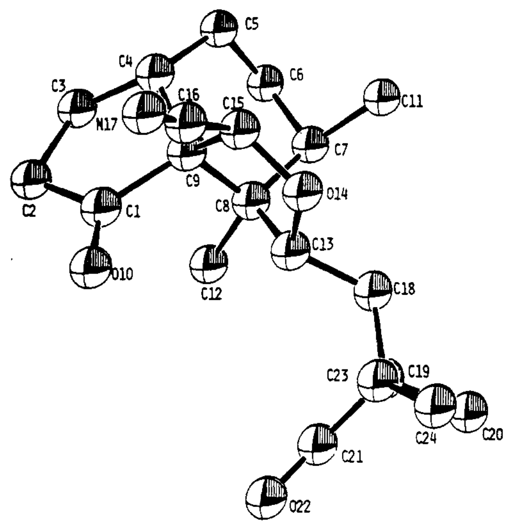
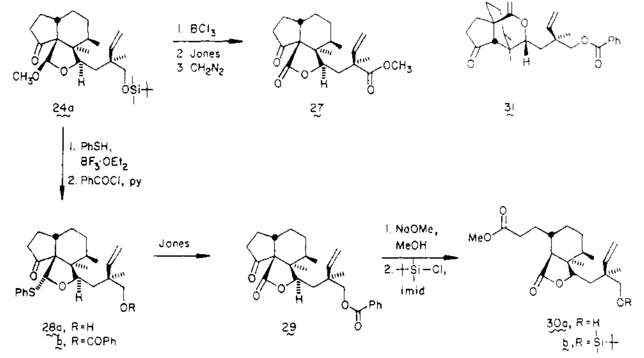


Figure 1. A computer-generated drawing of **34** derived from the X-ray coordinates with hydrogens omitted for clarity.

An early harbinger of the responsiveness of these photoproducts to chemical change materialized when the major isomer was found to undergo smooth conversion in 40% overall yield to a lactonic ester subsequently identified as **27**. More substantive suggestion that **24** had actually been produced photochemically arose by conversion to lactone **29**. Treatment of the acetal mixture with 1.5 equiv of thiophenol in methylene chloride followed by boron trifluoride etherate provided **28a**. Benzoylation of its unmasked hydroxyl group and subsequent exposure to Jones reagent completed the sequence. In **29**, it becomes important to recognize that the lactone and ketone carbonyl groups exist in a 1,3-relationship without an option for enolization at the central carbon atom. On this basis, the possibilities for base-induced ring cleavage appeared excellent and, indeed, sodium methoxide in methanol readily transformed **29** into **30a**. In the alternative structural option **31**, the same two carbonyl groups are 1,4-disposed and no opportunity for comparable cleavage of the cyclopentanone ring presents itself.



An independent line of investigation provided irrefutable evidence in support of these conclusions. Recent reports by both Johnson[21] and Olah[22] have described the preparation of α-alkoxy nitriles from acetals by means of trimethylsilyl cyanide and a Lewis acid. Application of this methodology to **24a** gave rise, after mild hydrolysis, to the cyano alcohol **32**. While the derived tosylate **33** did not lend itself to crystallographic analysis, aldehyde **34** formed

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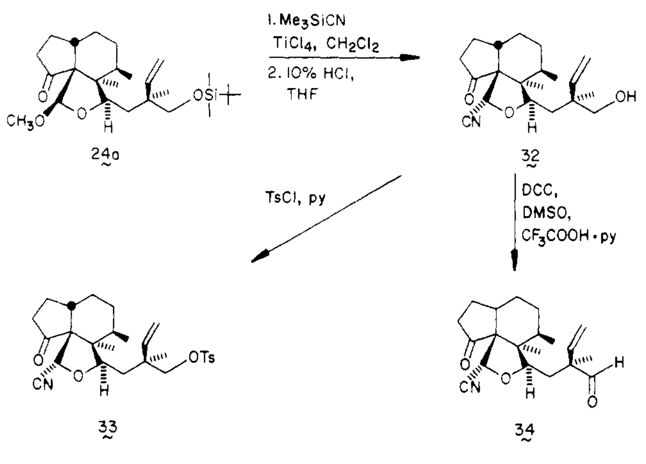
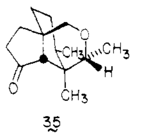


crystals suitable for X-ray diffraction studies. As seen in Figure 1, this analysis clearly revealed the regio- and stereochemical disposition of the lactone portion of the molecule and confirmed that photochemical closure of **19** and **22** had proceeded by unanticipated bonding to the α-carbon.

Hydrogen Atom Abstraction Occurs at the β-Carbon Atom. The mechanistic course of the formation of **21** and **24** can be most simply regarded as involving abstraction by the enone β-carbon of a CH_2O hydrogen, followed by collapse of the two resulting radical centers. No attempt has been made to substantiate the precise excited state(s) effectively responsible for these photochemical reactions. These cyclopentenones then serve as substrates in which a large discrimination exists between abstraction by the α- and β-carbon atom, with the latter being highly favored. Earlier, consideration had been given to the ground-state conformations of molecules of general formula **1**, where the methoxyl group was deemed to be capable of preferred alignment with the α-carbon. In the reactive excited state, the associated conformational modifications are evidently adequate to maximize proximity to the β-carbon instead.

MM2 calculations were performed on the simpler product prototypes **35** and **36** using Still's MACROMODEL program. The most stable (double-chair) conformer of the pyran derivative was found to be 1.13 kcal mol^{-1} more energetically favored than the furan, which possesses three conformations of closely comparable stability. These data suggest that the observed photocyclizations do not come under thermodynamic control. Rather, photoreactivity is likely controlled by the relative rates at which different radical pairs are formed.



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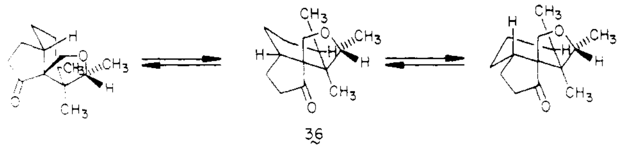
(37.35 kcal mol^{-1})



36

(39.46 kcal mol^{-1}) (38.47 kcal mol^{-1}) (39.30 kcal mol^{-1})

Given the limitations in the scope of this reaction, successful arrival at pleuromutilin or tiamulin from existing intermediates shall require that a different ploy be implemented to construct the functionalized eight-membered ring.

Experimental Section[23]

Photocyclization of 19. A glass tube was charged with **19** (30 mg, 0.0741 mmol) dissolved in methylene chloride (30 mL). The solution was deoxygenated with a stream of nitrogen for 20 min, and then the tube was sealed with a stopper. The reaction mixture was irradiated with a 450-W medium-pressure Hanovia mercury arc lamp. After 4 h, the two observed products were separated by MPLC (silica gel, 10% ethyl acetate in petroleum ether). The slower eluting material proved to be hydrolyzed **19**; the less polar substance, a colorless oil, was **21** (13 mg, 53%), $[\alpha]^{25}_{D}$ +67.0° (*c* 1.33, $CHCl_3$): IR ($CHCl_3$, cm^{-1}), 2970, 2885, 1731, 1710, 1460, 1420, 1385, 1265, 1077; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (dd, J = 17.4, 10.8 Hz, 1 H), 5.20 (d, J = 10.4 Hz, 1 H), 5.17 (d, J = 17.5 Hz, 1 H), 3.82 (dd, J = 9.0, 1.6 Hz, 1 H), 3.66 (AB q, $\Delta\nu$ = 59 Hz, J_{AB} = 8.6 Hz, 2 H), 2.49 (qd, J = 7.2, 2.5 Hz, 2 H), 2.32–1.68 (series of m, 10 H), 1.40–1.30 (m, 2 H), 1.31 (s, 3 H), 1.15 (d, J = 7.1 Hz, 3 H), 0.98 (t, J = 7.2 Hz, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 223.09, 213.55, 141.74, 115.34, 83.47, 72.65, 59.40, 53.75, 45.97, 37.47, 37.39, 35.50, 34.00, 31.40, 24.91, 24.48, 20.74, 19.94, 19.77, 17.02, 8.20 ppm; MS, *m/z* (M^+) calcd 332.2351, obsd 332.2336.

Preparation of 22. A solution of 2.56 g (7.70 mmol) of **4** in 135 mL of tetrahydrofuran and 135 mL of methanol was cooled in a 0 °C bath, while 1.17 g (30.7 mmol) of sodium borohydride was added. The reaction mixture was stirred at 0 °C for 2.5 h, poured into saturated sodium bicarbonate solution (600 mL), and extracted with methylene chloride (3 × 600 mL). The combined organic layers were dried, filtered, and concentrated in vacuo to leave a pale yellow oil. A small portion of the product was purified to provide an analytical sample of the alcohol: IR (film, cm^{-1}) 3400, 3080, 2920, 1685, 1625, 1380, 1030; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dd, J = 10.9, 17.6 Hz, 1 H), 5.10 (dd, J = 1.2, 10.9 Hz, 1 H), 5.06 (dd, J = 1.2, 17.6 Hz, 1 H), 4.51 (dd, J = 1.6, 8.0 Hz, 1 H), 4.49 ($^1/_2$ AB q, J = 6.0 Hz, 1 H), 4.44 ($^1/_2$ AB q, J = 6.1 Hz, 1 H), 3.44 ($^1/_2$ AB q, J = 11.3 Hz, 1 H), 3.31 ($^1/_2$ AB q, J = 11.4 Hz, 1 H), 3.19 (s, 3 H), 2.50–2.38 (m, 4 H), 2.37–2.10 (m, 3 H), 1.88–1.65 (m, 5 H), 1.13 (d, J = 6.8 Hz, 3 H), 1.11 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 209.02, 172.31, 145.59, 143.23, 112.84, 99.26, 82.87, 69.08, 55.75, 42.88, 41.74, 38.41, 36.98, 34.88, 29.71, 27.25, 26.24, 24.85, 20.49, 17.44 ppm.

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.04; H, 9.65.

The remainder of the material was admixed with 120 mL of dry methylene chloride, 3.20 mL of triethylamine (2.32 g, 23.4 mmol), and 3.52 mL (4.05 g, 15.3 mmol) of *tert*-butyldimethylsilyl triflate. The reaction mixture was stirred at room temperature for 3 h, poured into saturated sodium bicarbonate solution (300 mL), and extracted with methylene chloride (3 × 600 mL). The combined organic layers were dried, filtered, and concentrated in vacuo to leave a red oil. Column chromatography (silica gel, 5–20% ethyl acetate in petroleum ether) provided 2.30 g (67%) of **22**: $[\alpha]^{25}_{D}$ –63.0° (*c* 1.03, $CHCl_3$); IR (film, cm^{-1}) 3080, 2920, 1685, 1630, 1460, 1375, 1250, 1095, 1030, 835; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (dd, J = 11.0, 17.7 Hz, 1 H), 5.06 (dd, J = 1.3, 10.9 Hz, 1 H), 4.98 (dd, J = 1.4, 17.8 Hz, 1 H), 4.45 ($^1/_2$ AB q, J = 6.1 Hz, 1 h), 4.40 ($^1/_2$ AB q, J = 6.2 Hz, 1 H), 4.39 (d, J = 9.2 Hz, 1 H), 3.43 ($^1/_2$ AB q, J = 9.4 Hz, 1 H), 3.35 ($^1/_2$ AB q, J = 9.4 Hz, 1 H), 3.13 (s, 3 H), 2.50–2.30 (m, 4 H), 2.29–2.12 (m, 2 H), 1.95 (dd, J = 1.5, 14.8 Hz, 1 H), 1.77–1.70 (m, 3 H), 1.59 (dd, J = 8.0, 14.8 Hz, 1 H), 1.12 (dd, J = 6.7 Hz, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 0.89 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 207.72, 169.98, 144.92, 143.76, 113.00, 99.50, 83.19, 71.31, 55.29, 43.35, 42.27, 39.60, 37.37, 34.81, 29.59, 27.65, 26.19, 26.03, 25.13, 21.58, 18.58, 17.73, –5.23, –5.30 ppm; MS, the molecular ion peak was too transient for high-resolution measurement.

Photocyclization of 22. A total of 180 mg (0.40 mmol) of **22** was divided among eight oven-dried 16 × 150 mm Pyrex test tubes. Each was stoppered with a septum, evacuated, and filled three times with dry nitrogen. Each tube was then filled with an appropriate quantity of methylene chloride so that the concentration of the solution was 0.0045 M in enone. Acetone (0.05 mL) was introduced, and each tube was well mixed before being placed

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[23] The estimate of purity for all of the undistilled oils reported herein is >97% based upon TLC analysis (single spot) and spectral data.

in a Rayonet photochemical reactor and irradiated at 2537 Å for 4 h. The contents were combined and concentrated in vacuo to leave a yellow oil. Flash chromatography (silica gel, elution with 5% ethyl acetate in petroleum ether) provided 97.5 mg (54%) of **24a** and 15.7 mg (9%) of **24b**.

For **24a**: $[\alpha]^{25}_{D}$ -11.4° (*c* 0.63, $CHCl_3$); IR (film, cm^{-1}) 3080, 2950, 1720, 1465, 1380, 1095, 835; ^{1}H NMR (300 MHz, C_6D_6) δ 6.00 (dd, *J* = 10.9, 17.7 Hz, 1 H), 5.14 (dd, *J* = 1.3, 17.7 Hz, 1 H), 5.11 (dd, *J* = 1.4, 10.9 Hz, 1 H), 4.86 (s, 1 H), 4.15 (d, *J* = 8.3 Hz, 1 H), 3.51 ($^1/_2$ AB q, *J* = 9.4 Hz, 1 H), 3.41 ($^1/_2$ AB q, *J* = 9.4 Hz, 1 H), 3.22 (s, 3 H), 2.30 (m, 1 H), 2.13–1.95 (m, 3 H), 1.87–1.63 (m, 3 H), 1.57–1.44 (m, 3 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.25 (s, 3 H), 1.16–1.04 (m, 2 H), 0.97 (s, 9 H), 0.83 (s, 3 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) 221.14, 144.64, 113.52, 108.02, 81.25, 71.39, 62.64, 55.97, 45.51, 42.47, 37.97, 36.19, 34.91, 34.83, 26.18, 25.39, 24.82, 21.73, 21.57, 20.52, 18.58, 17.26, -5.27, -5.30 ppm; MS, the molecular ion peak was too transient for high-resolution measurement.

For **24b**: IR (film, cm^{-1}) 3080, 2920, 1730, 1620, 1465, 1455, 1245, 1090, 835; ^{1}H NMR (300 MHz, C_6D_6) δ 6.03 (dd, *J* = 10.8, 17.5 Hz, 1 H), 5.19–5.12 (m, 2 H), 4.83 (d, *J* = 9.2 Hz, 1 H), 4.76 (s, 1 H), 3.55 ($^1/_2$ AB q, *J* = 9.4 Hz, 1 H), 3.45 ($^1/_2$ AB q, *J* = 9.4 Hz, 1 H), 3.24 (s, 3 H), 2.12–1.89 (m, 4 H), 1.69 (d, *J* = 14.7 Hz, 1 H), 1.60–1.40 (m, 5 H), 1.36–1.16 (m, 2 H), 1.27 (s, 3 H), 1.14 (d, *J* = 7.1 Hz, 3 H), 0.98 (s, 12 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) 213.15, 144.76, 113.40, 110.50, 84.91, 71.36, 62.90, 56.07, 48.36, 42.34, 38.94, 38.52, 35.42, 34.40, 26.20, 25.97, 25.57, 21.84, 21.67, 20.68, 18.93, 18.59, -5.25, -5.23 ppm; MS, the molecular ion peak as too transient for high-resolution measurement.

Conversion of 24a to Keto Lactone 27. The major photoadduct **24a** (94.2 mg, 0.21 mmol) was dissolved in 9.5 mL of dry methylene chloride, cooled in a -78 °C bath, and treated with 0.63 mL of boron trichloride (1 M in methylene chloride, 0.63 mmol) via syringe. The reaction mixture was stirred at -78 °C for 1.5 h, quenched by the addition of saturated ammonium chloride solution (2 mL), and allowed to warm quickly to room temperature. The two-phase mixture was poured into brine (50 mL) and extracted with methylene chloride (2 × 80 mL). The combined organic layers were dried, filtered, and concentrated in vacuo to leave a colorless oil. The oil was placed in a 100-mL flask with 25 mL of acetone. The mixture was stirred as 70 drops of Jones reagent (7.0 g of CrO_3, 50 mL of H_2O, 6.1 mL of H_2SO_4) was added. The mixture was poured into brine (100 mL) and extracted with methylene chloride (2 × 150 mL). The combined organic layers were processed as above to leave a yellow oil, which was dissolved in 200 mL of ether and treated with 6 equiv of diazomethane. The ethereal solution was dried and concentrated in vacuo to leave a yellow oil. Flash chromatography (silica gel, 10–15% ethyl acetate in petroleum ether) provided 0.025 g (36%) of **27**: IR (film, cm^{-1}) 3080, 2920, 1760, 1720, 1630, 1455, 1225, 990, 920; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (dd, *J* = 10.8, 17.3 Hz, 1 H), 5.23 (d, *J* = 10.6 Hz, 1 H), 5.21 (d, *J* = 17.5 Hz, 1 H), 4.55 (dd, *J* = 1.1, 8.9 Hz, 1 H), 3.69 (s, 3 H), 2.86 (m, *J* = 5.4 Hz, 1 H), 2.36 (dd, *J* = 5.7, 10.0 Hz, 2 H), 2.27 (dd, *J* = 9.0, 15.2 Hz, 1 H), 2.16–1.68 (m, 7 H), 1.47–1.38 (m, 1 H), 1.40 (s, 3 H), 1.05 (s, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 214.89, 175.60, 175.54, 139.95, 115.67, 81.86, 62.52, 52.24, 48.00, 46.82, 38.12, 35.79, 34.98, 33.35, 25.89, 23.43, 20.00, 19.71, 19.66, 16.49 ppm; MS, molecular ion peak was too transient for high-resolution measurement.

Preparation of Hemithioketals 28a and 28b. A solution containing 0.277 g (0.615 mmol) of **24a** in 30 mL of methylene chloride was cooled in a -78 °C bath and 0.10 mL of thiophenol was introduced via syringe, followed by 3.0 mL of boron trifluoride etherate. The reaction mixture was stirred at -78 °C for 2 h, allowed to warm to -10 °C during 1 h, poured into saturated sodium bicarbonate solution (125 mL), and extracted with methylene chloride (2 × 150 mL). The combined organic layers were dried and concentrated in vacuo to leave a yellow oil. Flash chromatography (silica gel, 20% ethyl acetate in petroleum ether) provided 0.208 g (82%) of **28a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.38 (m, 2 H), 7.30–7.17 (m, 3 H), 5.87 (dd, *J* = 10.6, 17.9 Hz, 1 H), 5.20 (s, 1 H), 5.10–5.03 (m, 2 H), 4.59 (d, *J* = 9.2 Hz, 1 H), 3.62 ($^1/_2$ AB q, *J* = 11.5 Hz, 1 H), 3.40 ($^1/_2$ AB q, *J* = 11.5 Hz, 1 H), 2.59–2.51 (m, 3 H), 2.37 ($^1/_2$ AB q, *J* = 5.9 Hz, 1 H), 2.34 ($^1/_2$ AB q, *J* = 6.0 Hz, 1 H), 2.03–1.82 (m, 5 H), 1.75–1.69 (m, 1 H), 1.43–1.24 (m, 2 H), 1.17 (d, *J* = 7.1 Hz, 3 H), 1.03 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 217.87, 145.47, 137.36, 131.01, 128.94, 126.84, 112.60, 93.17, 83.71, 69.38, 63.99, 46.69, 41.41, 38.63, 37.16, 33.83, 25.42, 24.12, 20.52, 19.84, 19.53, 17.54 ppm; MS, the molecular ion peak was too transient for high-resolution measurement.

A solution of **28a** (0.400 g, 0.966 mmol) in 37 mL of pyridine was cooled in a 0 °C bath and treated with 0.17 mL (1.46 mmol) of benzoyl chloride. The mixture was stirred at room temperature for 11 h, poured into saturated sodium bicarbonate solution (120 mL), and extracted with methylene chloride (2 × 150 mL). The combined organic layers were dried and concentrated in vacuo to leave a yellow oil, column chromatography of which (silica gel, 20% ethyl acetate in petroleum ether) provided 0.375 g (75%) of **28b** as a colorless oil: IR (film, cm^{-1}) 3060, 2950, 1720, 1600, 1580, 1270, 1110, 1020, 1010, 710; ^{1}H NMR (300 MHz, C_6D_6) δ 8.17 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.15–7.02 (m, 5 H), 6.94–6.89 (m, 1 H), 5.83 (dd, *J* = 10.9, 17.5 Hz, 1 H), 5.30 (s, 1 H), 5.14–5.04 (m, 2 H), 4.82 (d, *J* = 8.9 Hz, 1 H), 4.42 ($^1/_2$ AB q, *J* = 10.8 Hz, 1 H), 4.26 ($^1/_2$ AB q, *J* = 10.8 Hz, 1 H), 2.22–1.94 (m, 4 H), 1.59–1.13 (m, 6 H), 1.27 (s, 3 H), 1.12–0.83 (m, 2 H), 1.02 (d, *J* = 7.1 Hz, 3 H), 0.69 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 216.20, 166.07, 143.88, 139.31, 132.71, 131.33, 130.89, 129.87, 129.20, 128.53, 126.69, 114.24, 93.99, 84.09, 71.74, 64.02, 47.02, 40.87, 38.71, 37.67, 34.70, 34.20, 25.68, 24.37, 20.75, 20.50, 19.88, 17.69 ppm; MS, the molecular ion peak was too transient for high-resolution measurement.

Oxidation of 28b. A solution containing 0.202 g (0.389 mmol) of **28b** in 20 mL of acetone was treated with excess Jones reagent at room temperature. When reaction was judged to be complete by TLC, the mixture was poured into water (150 mL) and extracted with methylene chloride (2 × 150 mL). The combined organic layers were dried and concentrated in vacuo to leave **29** as a colorless oil (0.146 g, 88%): IR (film, cm^{-1}) 3080, 3060, 2950, 1765, 1720, 1445, 1380, 1270, 1110, 1000, 920, 710; ^{1}H NMR (300 MHz, C_6D_6) δ 8.22–8.19 (m, 2 H), 7.21–7.10 (m, 3 H), 5.67 (dd, *J* = 10.8, 17.6 Hz, 1 H), 5.11 (d, *J* = 17.1 Hz, 1 H), 5.11 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 8.2 Hz, 1 H), 4.22 ($^1/_2$ AB q, *J* = 10.8 Hz, 1 H), 4.15 ($^1/_2$ AB q, *J* = 10.9 Hz, 1 H), 2.86–2.77 (m, 1 H), 1.99 (dd, *J* = 8.4, 15.1 Hz, 1 H), 1.90–1.84 (m, 2 H), 1.79–1.64 (m, 1 H), 1.57–1.39 (m, 3 H), 1.36–1.28 (m, 2 H), 1.24 (s, 3 H), 1.05–0.95 (m, 2 H), 0.92 (d, *J* = 7.1 Hz, 3 H), 0.70 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 214.41, 175.06, 166.06, 142.17, 132.92, 129.80, 128.67, 128.63, 115.76, 81.66, 71.72, 62.46, 46.61, 41.02, 38.01, 35.98, 34.19, 33.44, 25.88, 23.56, 20.14, 19.77, 19.59, 16.74 ppm.

Anal. Calcd for $C_{26}H_{32}O5$: C, 73.56; H, 7.60. Found: C, 73.64; H, 7.53.

Base-Induced Cleavage of 29. Lactone **29** (56 mg, 0.133 mmol) was dissolved in 12.5 mL of methanol containing 71.2 mg of sodium methoxide. The reaction mixture was heated at the reflux temperature for 1 h and allowed to cool to room temperature. Acidification with 10% hydrochloric acid (2.5 mL) was followed by pouring into water (60 mL) and extraction with methylene chloride (2 × 70 mL). The combined organic layers were dried and concentrated in vacuo to leave 0.037 g of impure **30a**. This material was dissolved in 8.4 mL of methylene chloride containing 0.09 mL (0.647 mmol) of triethylamine and 0.07 mL (0.305 mmol) of *tert*-butyldimethylsilyl triflate. The reaction mixture was stirred at room temperature for 1 h, poured into saturated sodium bicarbonate solution (30 mL), and extracted with methylene chloride (2 × 30 mL). The combined organic layers were dried and concentrated in vacuo to leave a colorless oil, column chromatography of which (silica gel, 10% ethyl acetate in petroleum ether) provided 33 mg (68%) of **30b**: IR (film, cm^{-1}) 3080, 2960, 2945, 2880, 2860, 1765, 1740, 1250, 1165, 1095, 840, 775; ^{1}H NMR (300 MHz, C_6D_6) δ 5.88 (dd, *J* = 10.9, 17.6 Hz, 1 H), 5.09 (dd, *J* = 1.3, 10.8 Hz, 1 H), 5.05 (dd, *J* = 1.3, 17.6 Hz, 1 H), 3.90 (d, *J* = 8.8 Hz, 1 H), 3.37 (s, 3 H), 3.35 ($^1/_2$ AB q, *J* = 9.4 Hz, 1 H), 3.29 ($^1/_2$ AB q, *J* = 9.4 Hz, 1 H), 2.21–2.04 (m, 3 H), 2.00–1.90 (m, 2 H), 1.78 (dd, *J* = 9.5, 14.8 Hz, 1 H), 1.66–1.51 (m, 2 H), 1.48 (d, *J* = 7.0 Hz, 1 H), 1.41–1.29 (m, 1 H), 1.26–1.18 (m, 1 H), 1.10 (s, 3 H), 0.95 (s, 9 H), 0.92 (d, *J* = 7.1 Hz, 3 H), 0.81 (s, 3 H), 0.77–0.69 (m, 2 H), -0.02 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 176.87, 173.15, 143.64, 114.24, 84.64, 71.64, 51.90, 51.03, 44.53, 42.60, 37.71, 35.20, 34.25, 32.10, 29.86, 28.18, 27.34, 26.13, 26.09, 20.15, 18.46, 16.59, -5.35, -5.41 ppm;

MS, the molecular ion peak was too transient for high-resolution measurement.

Cyanation of 24a. A solution of **24a** (49.5 mg, 1.10 mmol) in 55 mL of dry methylene chloride was treated with trimethylsilyl cyanide (0.54 g, 5.47 mmol) and cooled in a −78 °C bath with stirring. Titanium tetrachloride (3.30 mL of a 1.0 M solution in CH_2Cl_2, 3.3 mmol) was introduced and the reaction mixture was stirred at −78 °C for 1 h, then allowed to warm slowly to 0 °C during 2.5 h. The solution was poured into saturated sodium bicarbonate solution (120 mL) and extracted with methylene chloride (2 × 150 mL). The combined organic layers were dried and concentrated in vacuo to leave a yellow-white suspension, which was dissolved in 50 mL of tetrahydrofuran and 25 mL of 10% hydrochloric acid and stirred at room temperature for 1 h. Pouring into saturated sodium bicarbonate solution (300 mL) followed by extraction with methylene chloride (2 × 200 mL) was followed by drying and concentration in vacuo. The resulting yellow oil was flash chromatographed (silica gel, 30% ethyl acetate in petroleum ether) to provide 0.228 g (62%) of **32** as a colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 5.79 (dd, J = 10.3, 17.9 Hz, 1 H), 5.07–5.02 (m, 2 H), 4.49 (d, J = 8.7 Hz, 1 H), 4.09 (s, 1 H), 3.36 ($^1/_2$ AB q, J = 10.9 Hz, 1 H), 3.28 ($^1/_2$ AB q, J = 10.9 Hz, 1 H), 1.89–1.76 (m, 3 H), 1.65–1.53 (m, 2 H), 1.46–1.05 (m, 6 H), 1.00 (s, 3 H), 0.89–0.77 (m, 2 H), 0.78 (d, J = 7.2 Hz, 3 H), 0.51 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 216.20, 144.58, 117.68, 113.85, 85.51, 70.34, 70.04, 62.32, 46.37, 41.98, 37.73, 36.44, 34.17, 33.42, 24.92, 23.64, 20.50, 20.02, 19.00, 16.57 ppm; MS, the molecular ion peak was too transient for high-resolution measurement.

Tosylation of 32. A solution of **32** (0.0056 g, 0.17 mmol) in 5 mL of methylene chloride at 0 °C was treated with 0.07 mL (0.50 mmol) of triethylamine, 0.065 g (0.34 mmol) of *p*-toluenesulfonyl chloride, and 0.023 g (0.19 mmol) of 4-(*N,N*-dimethylamino)pyridine. The flask was placed in a 0 °C refrigerator and allowed to stand for 36 h. The mixture was poured into saturated sodium bicarbonate solution (45 mL) and extracted with methylene chloride (2 × 50 mL). The combined organic layers were dried and concentrated in vacuo to leave a colorless oil, flash chromatography of which (silica gel, 30% ethyl acetate in petroleum ether) provided 60 mg (72%) of **33** as fine colorless plates, mp 172–173 °C (from hexane–ethyl acetate): ^{1}H NMR (300 MHz, C_6D_6) δ 7.78 (d, J = 8.3 Hz, 2 H), 6.76 (d, J = 8.1 Hz, 2 H), 5.59 (dd, J = 11.0, 17.5 Hz, 1 H), 4.96 (dd, J = 0.7, 10.7 Hz, 1 H), 4.93 (dd, J = 0.7, 17.5 Hz, 1 H), 4.36 (dd, J = 1.3, 8.9 Hz, 1 H), 4.05 (s, 1 H), 3.86 ($^1/_2$ AB q, J = 9.2 Hz, 1 H), 3.81 ($^1/_2$ AB q, J = 9.3 Hz, 1 H), 1.89–1.71 (m, 2 H), 1.86 (s, 3 H), 1.64–1.49 (m, 1 H), 1.36–1.02 (m, 9 H), 0.95 (s, 3 H), 0.76 (d, J = 7. Hz, 3 H), 0.47 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 216.13, 144.39, 141.64, 134.08, 129.92, 128.20, 117.64, 115.39, 85.06, 76.85, 70.31, 62.20, 46.41, 40.52, 37.69, 36.41, 34.12, 33.30, 24.90, 23.62, 21.18, 20.51, 19.94, 18.98, 16.47 ppm.

Anal. Calcd for $C_{27}H_{35}NSO_5$: C, 66.78; H, 7.26. Found: C, 66.53; H, 7.27.

Oxidation of 32. The nitrile alcohol **32** (228 mg, 0.689 mmol) was added to 26 mL of dry benzene containing 0.29 mL of dry dimethyl sulfoxide (0.319 g, 4.09 mmol), 0.425 g (2.06 mmol) of dicyclohexylcarbodiimide, and 0.133 g, (0.689 mmol) of pyridinium trifluoroacetate. The reaction mixture was stirred at room temperature for 3 h, poured into saturated sodium bicarbonate solution (120 mL), and extracted with methylene chloride (2 × 150 mL). The combined organic layers were dried and concentrated in vacuo to leave a white solid, flash chromatography of which (silica gel, 20% ethyl acetate in petroleum ether) provided 0.175 g (77%) of **34** as colorless needles, mp 130–131 °C (from hexanes–methylene chloride); $[\alpha]^{25}_D$ +96.7° (c 0.96, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3080, 2940, 2230, 1720, 1625, 1465, 1380, 1060, 930; ^{1}H NMR (300 MHz, C_6D_6) δ 9.16 (s, 1 H), 5.48 (dd, J = 10.7, 17.5 Hz, 1 H), 5.01 (dd, J = 0.5, 10.7 Hz, 1 H), 4.91 (dd, J = 0.5, 17.5 Hz, 1 H), 4.37 (dd, J = 1.8, 9.6 Hz, 1 H), 4.05 (s, 1 H), 1.94–1.77 (m, 3 H), 1.55–1.46 (m, 2 H), 1.31–1.05 (m, 5 H), 1.12 (s, 3 H), 0.80–0.72 (m, 2 H), 0.75 (d, J = 7.2 Hz, 3 H), 0.47 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 216.30, 201.13, 138.68, 117.64, 117.50, 84.92, 70.33, 62.37, 52.27, 46.36, 37.70, 36.45, 33.41, 32.89, 24.94, 23.67, 20.55, 19.08, 17.98, 16.38 ppm.

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26. Found: C, 72.80; H, 8.30.

X-ray Crystal Structure Analysis of 34. Suitable crystals of **34** ($C_{20}H_{27}NO_3$) for X-ray diffraction studies formed with space group symmetry of $P2_12_12_1$ and cell constants of a = 13.760 (3) Å, b = 14.920 (3) Å, and c = 8.859 (2) Å for Z = 4 and a calculated density of 1.203 g/cm^3. Of the 1412 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1218 were observed ($I > 3\sigma I$). The structure was solved with a direct methods approach and difference Fourier analysis and refined using full-matrix least-squares tecniques.[24] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of .052. No abnormally short intermolecular contacts were noted. Tables I, II, and III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **34** from the final X-ray coordinates showing the correct stereochemistry.

Acknowledgment. This research was supported by grants from the National Institutes of Health (GM 30827) and the Eli Lilly Company. Quantities of pleuromutilin and tiamulin were generously provided by Dr. Russ Buchman (SDS Biotech), Dr. R. Nagarajan (Eli Lilly Company), and Dr. Heinz Berner (Sandoz Forschungsinstitut), whom we thank. The MM2 calculations were performed by George Maynard.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **34** (4 pages). Ordering information is given on any current masthead page.

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[24] The following library of crystallographic programs was used: SHELXS-86, Sheldrick, G. M., University of Gottingen, Gottingen, West Germany, 1986. ORTEP-II, Johnson, C. K., Oak Ridge National Laboratory, Oak Ridge, TN, 1970. SDP Plus V1.1, Okaya, Y.; Frenz, B. A. (B. A. Frenz and Associates), College Station, TX, 1984.