m/z 496.3318, found m/z 496.3304.

Phosphonoacetate 28. To a solution of **27** (87 mg, 0.175 mmol) in 4.5 mL of dry THF was added a hexane solution of *n*-BuLi (0.52 mmol) under argon at −78 °C. After stirring for 20 min, a solution of methyl chloroformate (50 mg, 0.52 mmol) in 1.5 mL of dry THF was added at −78 °C. After 30 min, water (30 mL) was added and the mixture was extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and then concentrated in vacuo. The residue was chromatographed on 10 g of silica gel (CH_2Cl_2) to afford **28** (75 mg, 77%) as a colorless oil: IR (neat) 1740, 1640, 1256, 1050, 1030, 882 cm^{-1}; ^1H NMR δ 1.57 (s, 6 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 3.01 (m, 1 H), 3.76 (s, 3 H), 3.78 (d, J = 10.7 Hz, 3 H), 3.80 (d, J = 10.7 Hz, 3 H), 3.82 (m, 2 H), 3.95 (m, 2 H), 4.76–4.85 (m, 3 H), 5.02–5.18 (m, 3 H); MS, m/z 554(M^+), 73 (b.p.). Anal. Calcd for $C_{30}H_{51}O_7P$: C, 64.94; H, 9.27. Found: C, 64.64; H, 9.12.

Hydrolysis of 28 to 29. The acetal **28** (70 mg) was converted into the aldehyde **29** (59 mg, 91%) by the same manner as described in the preparation of **20**. **29**: colorless oil: IR (neat) 1740, 1728, 1642, 1256, 1050, 1025, 885 cm^{-1}; ^1H NMR δ 1.58 (s, 3 H), 1.60 (s, 3 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 3.00 (m, 1 H), 3.76 (s, 3 H), 3.78 (d, J = 11.0 Hz, 3 H), 3.79 (d, J = 11.0 Hz, 3 H), 4.83 (br s, 1 H), 4.87 (br s, 1 H), 5.02–5.15 (m, 3 H), 9.66 (t, J = 2.4 Hz, 1 H); MS, m/z 510 (M^+), 182 (b.p.); HRMS, calcd for $C_{28}H_{47}O_6P$ m/z 510.3110, found m/z 510.3110.

Intramolecular Wadsworth–Emmons Olefination of 29. A solution of **29** (30 mg, 0.059 mmol) in 30 mL of dry DME was heated at 80 °C under argon, and sodium hydride (60% mineral oil dispersion, 12 mg, 0.3 mmol) was added with stirring. After being stirred at 80 °C for 30 min, the reaction mixture was poured into ice–water and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The product showed mainly two spots on TLC. These were separated by medium-pressure liquid chromatography. Elution with benzene–hexane (1:2) gave **30** (11.8 mg, 52%) as a colorless oil. Further elution with benzene–hexane (1:1) afforded **6** (5.5 mg, 24%) whose ^1H and ^{13}C NMR spectra were identical with those of the methyl ester of natural ceriferic acid I (**30**): IR (neat) 1720, 1640, 880 cm^{-1}; ^1H NMR δ 1.53 (s, 3 H), 1.57 (s, 3 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 3.73 (s, 3 H), 4.77 (br s, 1 H), 4.79 (br s, 1H), 4.98 (br t, J = 7.2 Hz, 1 H), 5.05 (br t, J = 6.3 Hz, 1 H), 5.12 (br t, J = 7.2 Hz, 1 H), 5.85 (t, J = 7.7 Hz, 1 H); ^{13}C NMR δ 15.1 (q), 17.7 (q × 2), 23.7 (t), 25.6 (t), 25.7 (q), 26.7 (t), 29.0 (t), 34.0 (t × 2), 34.2 (t × 2), 39.4 (t), 44.2 (d), 51.0 (q), 108.7 (t), 122.3 (d), 124.3 (d), 125.1 (d), 130.9 (s), 131.5 (s), 133.7 (s), 134.6 (s), 141.3 (d), 152.8 (s), 168.5 (s); MS, m/z 384 (M^+), 135 (b.p.); HRMS, calcd for $C_{26}H_{40}O_2$ m/z 384.3028, found m/z 384.3033.

Acknowledgment. We are gratefull to Dr. Yoko Naya, Suntory Institute for Bioorganic Chemistry, for the spectra of an authentic sample of methyl ceriferate I. We also thank Dr. Masao Toyota of this university for the measurement of high-resolution mass spectra.

Registry No. (±)-**6**, 107655-35-6; **9**, 95531-81-0; **10**, 81027-74-9; (±)-**11**, 113219-29-7; **12**, 113219-30-0; **13**, 95531-99-0; **14**, 35162-74-4; (±)-**14** (bromohydrin), 113219-35-5; (±)-**15**, 113219-31-1; (±)-**16**, 113219-32-2; **17**, 113219-33-3; (±)-**18**, 113219-34-4; **19**, 107553-96-8; **20**, 107554-01-8; (*E*)-**21**, 107554-03-0; (*Z*)-**21**, 107553-97-9; (*E*)-**22**, 107553-98-0; (*Z*)-**22**, 107554-12-1; (*E*)-**22** (vinyl ether), 107554-04-1; (*Z*)-**22** (vinyl ether), 107553-99-1; (±)-**23**, 107554-05-2; (±)-**24**, 107574-35-6; (±)-**25**, 107554-06-3; (±)-**25** (R = Ms), 107554-11-0; (±)-**26**, 107554-08-5; (±)-**27**, 107554-09-6; **28**, 107554-10-9; **29**, 107569-40-4; (±)-**30**, 107655-36-7; $BnO(CH_2)_3OH$, 4799-68-2; $BnO(CH_2)_2CHO$, 19790-60-4; $Ph_3P{=}C(CH_3)CO_2Et$, 5717-37-3; $(CH_3)_2C{=}CH(CH_2)_2Br$, 2270-59-9; $(EtO)_2P(O)CH_2CO_2Et$, 867-13-0; $CH_3P(O)(OMe)_2$, 756-79-6; homofurnesyl iodide, 113219-28-6.

Supplementary Material Available: Experimental procedures for the preparation of compounds **9**, **10**, **12**, **13**, **15**, **16**, and **17** (5 pages). Ordering information is given on any current masthead page.

(+)-Pleuromutilin Synthetic Studies. Degradative and de Novo Acquisition of a Levorotatory Tricyclic Lactone Subunit

Leo A. Paquette,* Paul E. Wiedeman,[1] and Philip C. Bulman-Page[2]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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The diterpene antibiotics pleuromutilin and tiamulin have been degraded to the common levorotatory lactone **3** in four steps. This important intermediate has been constructed in optically active condition from simple starting materials. The key elements of this synthesis were (i) stereoselective introduction of the second methyl group in **8** and regiospecific cyclopentenone annulation of this oxocyclohexanecarboxylate ester, (ii) stereocontrolled attachment of the lactone ring to give **20**, and (iii) proper introduction of the methyl and vinyl substituents α to the lactone carbonyl functionality in **20**. This and other synthetic methodologies have been utilized to prepare stereoisomers of **3** that could potentially lead to unnatural pleuromutilins by reconstruction of the cyclooctane ring.

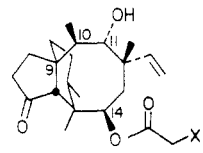
Pleuromutilin (**1a**) was isolated in the early 1950's by Kavanagh and co-workers from several species of basidiomycetes including *Pleurotus mutilus*, *Pleurotus passeckerianus*, and *Drosophilia substrata*.[3] From the outset, the colorless crystalline substance attracted considerable attention as a consequence of its significant in vitro antibiotic activity against gram-positive bacteria and its low animal toxicity. In the intervening years, several additional pleuromutilins have been uncovered. The majority possess a structurally modified glycolic ester subunit that has either been esterified with a fatty acid[4] or involved in a glycosidic linkage with α-D-xylose.[5] Other congeners possess one or more additional hydroxyl groups.[5,6]

The clinical efficacy of **1a** has prompted a great deal of effort toward understanding its mechanism of action and improving its potency.[7] As a consequence of a systematic

(1) National Science Foundation Predoctoral Fellow, 1981–1984.
(2) NATO Postdoctoral Fellow of the Science and Engineering Research Council, 1981–1983.
(3) Kavanagh, F.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 570; **1952**, *38*, 555.
(4) Knauseder, F.; Brandl, E. *J. Antibiot.* **1975**, *29*, 125.
(5) Michel, K. H.; Dorman, D. E.; Occolowitz, J. L. *Curr. Chemother. Infect. Dis. Proc. Int. Congr. Chemother., 11th* **1979**, *1*, 479.
(6) Berner, H.; Vyplel, H.; Schulz, G.; Stuchlik, P. *Tetrahedron* **1983**, *39*, 1317.

0022-3263/88/1953-1441$01.50/0

structure–activity investigation, it is presently recognized that the cyclopentanone ring is essential, the C-11 hydroxyl group must be neither esterified nor oxidized, and the C-14 hydroxyl must be acylated. The concensus view at present



1g, X = OH
b, X = $SCH_2CH_2NEt_2$

is that potency is intimately linked to the nature of this acyl group. The derivative currently in veterinary use is tiamulin (**1b**).[7,8] In this connection, **1a** and **1b** are both active against the growth of the mycoplasms and act as protein synthesis inhibitors. Research continues with a view to improving efficacy still further and to comprehending the unusual chemical reactivity of these compounds.[9]

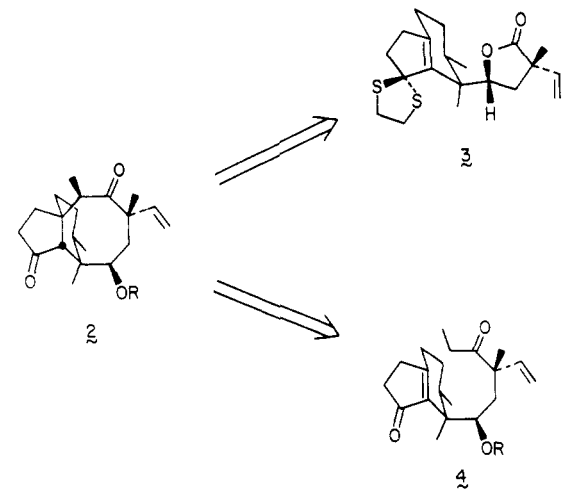
The structure of **1a** was elucidated during the 1950's and 1960's. Following a preliminary chemical study by Anchel who determined the molecular formula to be $C_{22}H_{34}O_5$,[10] two research groups headed by Arigoni[11] and by Birch[12] independently demonstrated the diterpene to be constituted of a rather rigid tricyclic carbon network having eight stereogenic centers, seven of which are positioned consecutively around the eight-membered ring. Ultimate reaffirmation of their assignment was achieved much later (1975) by X-ray crystallographic analysis of a bromoacetate derivative.[13] As can be seen, pleuromutilin also carries three quaternary stereogenic centers and is assembled biosynthetically from *all-trans*-geranylgeranyl pyrophosphate in spectacular fashion.[11,12,14]

Pleuromutilin represents a challenging synthetic target. Its five-, six-, and eight-membered rings all share two carbon atoms. The cyclohexane and cyclooctane rings also have a third tetrahedral center in common. To date, a preliminary approach[15] and an elegant total synthesis of racemic **1a** have appeared.[16]

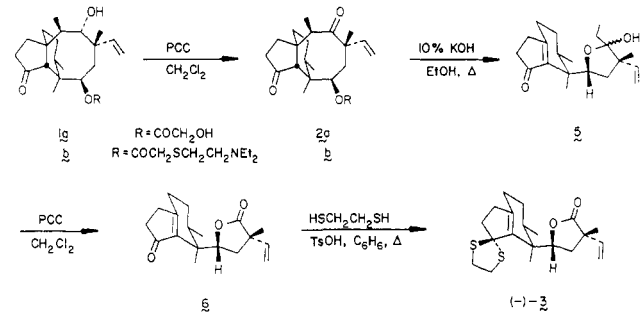
Synthetic Plan

Certainly the most provocative feature of structure **1** is the medium-sized ring. We have proceeded to consider an attempt at establishing the C-9/C-10 bond late in our synthetic sequence (Scheme I). This ploy was clearly recognized to be an example of a protocol where one of the expectedly more difficult transformations is deferred to virtually last position. While a resolution of this specific issue was certain to be nontrivial, the possibility of taking advantage of a relay synthesis loomed as an irresistable motivating factor.

Scheme I



Scheme II



Particularly concise versions of our plan to prepare **1a** in enantioselective fashion involved initial retrograde Michael fragmentation of a pleuromutilone (**2**) to **4** or somewhat more deep-seated degradation to lactone **3**. If proper reintroduction of an ethyl group into **3** could be achieved conveniently, **4** or a formal equivalent of this diketone would be available for an orderly reconstruction of the pivotal cyclooctane core.

Following a review of the degradative studies undertaken previously by Arigoni on dihydro analogues of these substrates,[11] no untoward features inherent in the relay component of the plan (Scheme I) were discerned. It was, of course, equally necessary to develop in tandem an independent synthesis of **3** via a sequence guaranteed to properly integrate its four stereocenters in an absolute sense. A solution to this aspect of the overall approach is also detailed herein.[17]

Discussion of Results

Degradative Studies. The projected relay approach was expected to offer two advantages. First, comparison of the degradation product with the synthetic material would ensure at a reasonably early period that the several stereogenic centers have been properly installed in a relative and also absolute sense. Second, the degradative route would, if sufficiently short, serve as an important source of advanced intermediates to assist in completion of the synthesis. Both features have been realized, since

(7) Hogenauer, G. In *Mechanism of Action of Antibacterial Agents*; Kahn, R. E., Ed.; Springer-Verlag: New York, 1979; pp 344–360 and references cited therein.

(8) The significantly enhanced activity of tiamulin is described in: (a) Egger, H.; Reinshagen, H. *J. Antibiot.* **1976**, *29*, 915, 923. (b) Drews, J.; Georgopoulos, A.; Laber, G.; Schultze, E.; Unger, J. *Antimicrob. Agents Chemother.* **1975**, *7*, 507. (c) Laber, G.; Schultze, E. *Ibid.* **1975**, *7*, 517.

(9) Berner, H.; Vyplel, H.; Schulz, G. *Tetrahedron* **1987**, *43*, 765 and earlier papers by the Sandoz group cited therein.

(10) Anchel, M. *J. Biol. Chem.* **1952**, *199*, 133.

(11) (a) Arigoni, D. *Gazz. Chim. Ital.* **1962**, *92*, 884. (b) Arigoni, D. *Pure Appl. Chem.* **1968**, *17*, 331. (c) Naegeli, P. Ph.D. Thesis, ETH, Zurich, 1961. (d) Buzzolini, M. Ph.D. Thesis, ETH, Zurich, 1966. (e) Bonavia, G. Ph.D. Thesis, ETH, Zurich, 1968. (f) Hasler, H. Ph.D. Thesis, ETH, Zurich, 1979.

(12) (a) Birch, A. J.; Cameron, D. W.; Holzapfel, C. W.; Rickards, R. W. *Chem. Ind. (London)* **1963**, 374. (b) Birch, A. J.; Holzapfel, C. W.; Rickards, R. W. *Tetrahedron, Suppl.* **1966**, *8*, 359.

(13) Dobler, M.; Dürr, B. G. *Cryst. Struct. Commun.* **1975**, *4*, 259.

(14) Cane, D. E. *Tetrahedron* **1980**, *36*, 1109.

(15) Kahn, M. *Tetrahedron Lett.* **1980**, 4547.

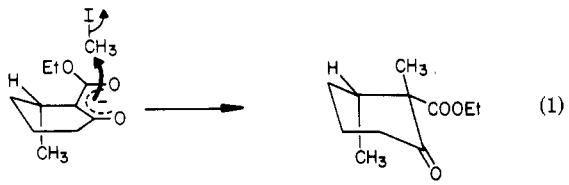
(16) (a) Gibbons, E. G. *J. Org. Chem.* **1980**, *45*, 1540. (b) Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767.

(17) For preliminary reports on selected aspects of this work, see: (a) Paquette, L. A.; Wiedeman, P. E. *Tetrahedron Lett.* **1985**, 1603. (b) Paquette, L. A., Bulman-Page, P. C. *Ibid.* **1985**, 1607. (c) Paquette, L. A.; Wiedeman, P. E.; Bulman-Page, P. C. *Ibid.* **1985**, 1611.

the transformation of **1a** or **1b** into **3** requires only four laboratory steps (Scheme II).

Oxidation of **1a** and **1b** with pyridinium chlorochromate (PCC) efficiently gave rise to pleuromutilone (**2a**) and tiamulone (**2a**) in excellent yield (86–97%) without affecting the glycolate or thioglycolate funtionality. Heating these intermediates with 10% potassium hydroxide in ethanol initiated a cascade of three chemical reactions. Following kinetically controlled ester hydrolysis, the cyclooctanone ring ruptured by means of a retrograde Michael reaction, and the hydroxy diketone so generated was cyclized to hemiketal **5** (83%). On subsequent PCC oxidation of **5**, the ethyl group was cleaved smoothly. This process, which has been encountered previously in closely related lactols,[11c,d] probably proceeds by C → O migration of the alkyl group in the chromate ester with ejection of $HCrO_3^-$. The rearranged oxonium-stabilized cation then captures water and acetaldehyde is ultimately lost. The four stereocenters present are not perturbed by this sequence of events. Dithioketalization of **6** secured **3**, which proved to be a levororotatory substance, $[\alpha]^{20}_D$ −6.9° ($CHCl_3$). Analysis of its 300-MHz ^1H NMR spectrum (in $CDCl_3$) showed the three methyl absorptions to be clearly defined at δ 1.52 (s), 1.36 (s), and 1.04 (d).

Construction and Resolution of the Tetrahydroindanone Segment. Conveniently, the cyclohexanone carboxylate **7** is readily available.[18] The expectation was that methylation of its enolate anion could be performed stereoselectively. In the course of their syntheses of aristolone and bakkenolide A, respectively, Piers[19] and Evans[20] demonstrated that alkylation of 2,3-dimethyl-6-[(*n*-butylthio)methylene]cyclohexanone afforded a cis/trans mixture in an approximate 4:1 ratio. In the present instance, the methyl group is to be introduced last, and a reversal in stereoisomer production was, of course, anticipated. As shown in eq 1, the desired stereochemical outcome does not require the pendant C-3 methyl substituent to be projected pseudoaxially as also dictated by A-strain factors.[21] To the extent that some semblance of

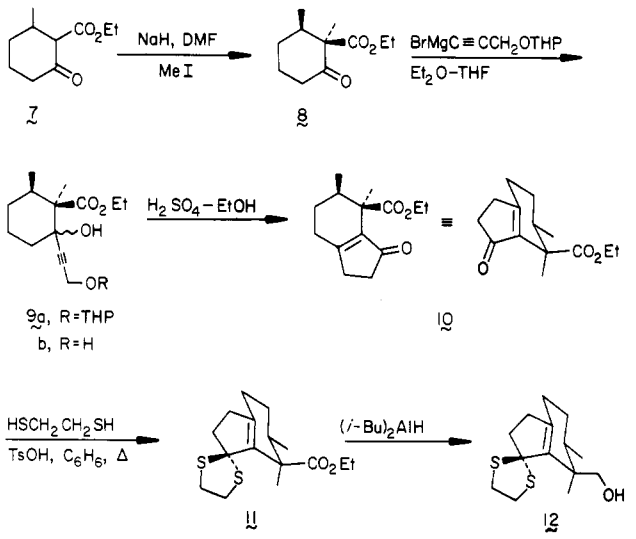


(1)

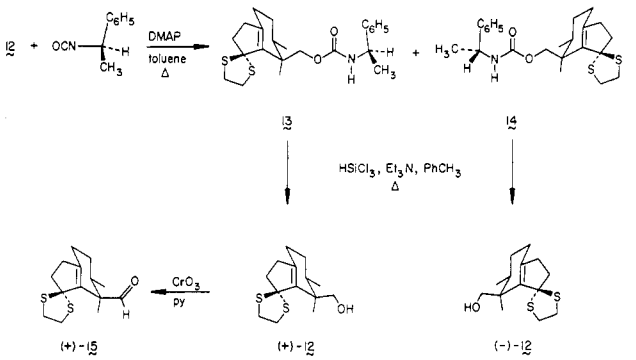
this conformational character is maintained as the two possible transition states are approached, axial entry of the methyl iodide from above-plane should be favored.

In practice (Scheme III), there was obtained a three-component mixture consisting (VPC analysis) of the desired **8** (81%), its cis counterpart (12%), and dimethylated product (7%). Proper separation of **8** on a relatively large scale was accomplished by spinning-band distillation. At this juncture, regioselective cyclopentenone annulation was required. As a result of the substantial steric crowding about the ketone carbonyl in **8**, attempts to effect condensation with diphenylsulfonium cyclopropylide[22] or 1,1-dichloroallyllithium[23] met with complete failure. However, the significantly reduced size of the Grignard

Scheme III



Scheme IV



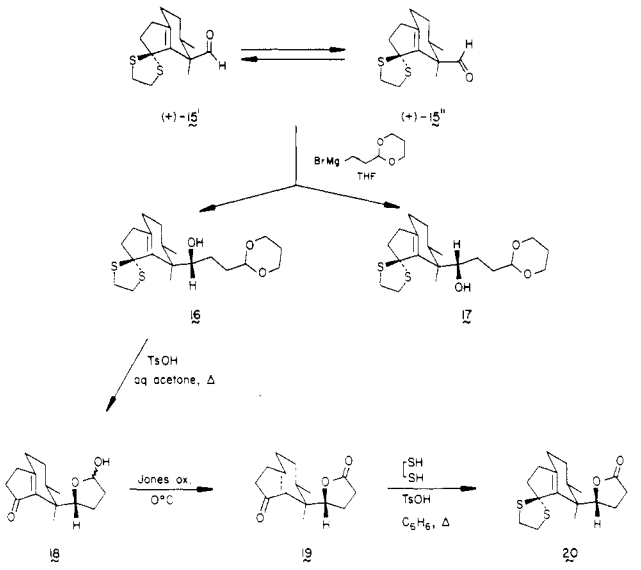
reagent derived from the tetrahydropyranyl ether of propargyl alcohol[24] permitted chemoselective addition to **8** with formation of diastereomers **9a** in 71% yield. By analogy to the original observations of Raphael,[25] both **9a** and **9b** underwent smooth acid-catalyzed cyclization to give **10**.

Crafting of the carbethoxy function into the requisite side chain demanded prior masking of the ketone functionality in **10**. When **10** proved recalcitrant to all attempts at ketalization,[26] recourse was made to more nucleophilic sulfur reagents. Although methyl mercaptan and (mercaptomethyl)trimethylsilane also did not engage **10** into reaction, 1,2-ethanediol provided **11** efficiently (98%) and made possible subsequent Dibal-H reduction to alcohol **12**.

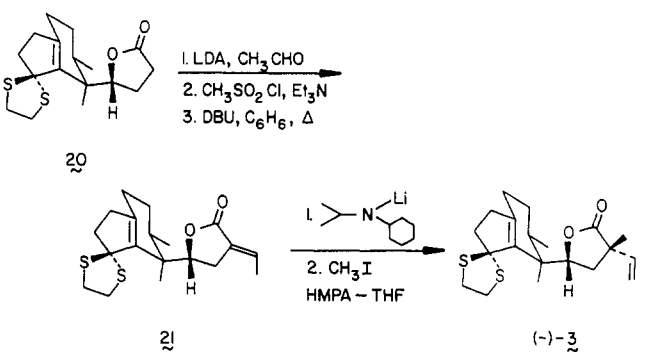
Reaction of **12** with (*R*)-(+)-α-methylbenzyl isocyanate[27] delivered the carbamates **13** and **14**, which proved to be

(18) Mukerjee, S. *J. Indian Chem. Soc.* **1962**, *39*, 347.
(19) Piers, E.; Britton, R. W.; DeWaal, W. *Can. J. Chem.* **1969**, *47*, 4307.
(20) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453.
(21) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(22) Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328.
(23) Hiyama, T.; Shinoda, M.; Nozaki, H. *Tetrahedron Lett.* **1978**, 711.
(24) Claesson, A.; Olsson, L.-I.; Bogentoft, C. *Acta Chem. Scand.* **1973**, *27*, 2941.
(25) MacAlpine, G. A.; Raphael, R. A.; Shaw, A.; Taylor, A. W.; Wild, H.-K. *J. Chem. Soc., Chem. Commun.* **1974**, 834. See also: Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 1226. Hiyama, T.; Shinoda, M.; Saimoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2747.
(26) Only starting material was recovered from reactions with ethylene glycol and 1,3-propanediol in the presence of a variety of protic catalysts. No reaction was observed in attempts to form the dimethyl acetal from trimethyl orthoformate, likewise with an assortment of catalysts [Meskins, F. A. J. *Synthesis* **1981**, 501. Van Allen, J. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 21. Mackenzie, C. A.; Stocker, J. H. *J. Org. Chem.* **1955**, *20*, 1695. Schwenk, E.; Fleischer, G.; Whitham, B. *J. Am. Chem. Soc.* **1938**, *60*, 1702]. Similar negative results were obtained under neutral conditions employing 1,2-bis(trimethylsiloxy)ethane and trimethylsilyl trifluoromethanesulfonate [Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 1357].
(27) (a) Cairns, T. L. *J. Am. Chem. Soc.* **1941**, *63*, 871. (b) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904. (c) Paquette, L. A.; Doehner, R. F. *Ibid.* **1980**, *45*, 5105.

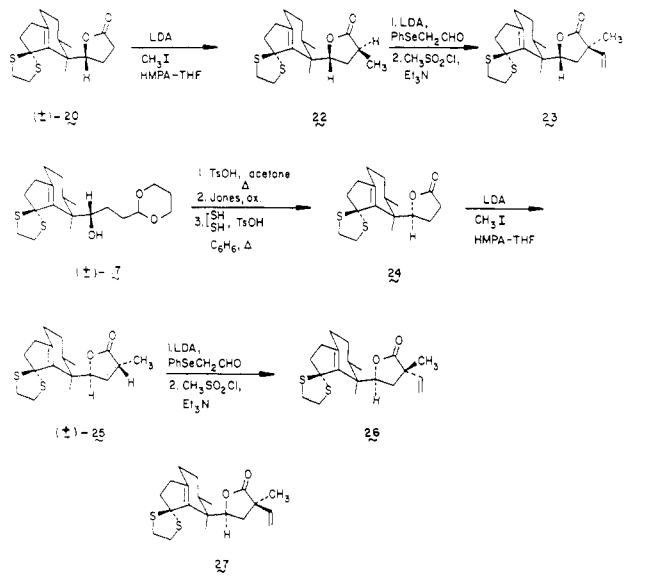
Scheme V



Scheme VI



Scheme VII



separable by high-pressure chromatography on silica gel (Scheme IV). Recycling and band-shaving techniques had to be implemented for maximum efficiency in this operation. Notwithstanding, **13** was not completely separated from **14**. By exposure of the individual purified carbamates to trichlorosilane,[28] cleavage to the enantiomerically related alcohols (+)- and (−)-**12** could be achieved without affecting the dithiolane functionality.

The extent of enantiomeric purity was established by ^{1}H NMR analysis in the presence of tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) as chiral shift reagent. While the enrichment for (−)-**12** was seen to be 56% ee, (+)-**12** was obtained in somewhat improved condition (78% ee).[29]

With elaboration of the enantiomers of **12**, construction of the indanone part structure in optically active condition had been achieved in relatively few steps. This structural component contains 12 of the 20 carbon atoms present in pleuromutilin. Additionally, two pivotal stereogenic centers have been set. Since it was unknown which enantiomer of **12** was related to pleuromutilin, both were carried forward in the scheme subsequently to be outlined. For simplicity, only the further elaboration of (+)-**12** is described here since it constitutes the ultimate proper link with the degraded natural product.[30]

Elaboration of the Pendant Lactone Functionality. The oxidation of (+)-**12** to aldehyde **15** was best implemented by Collins oxidation.[31,32] Molecular models indicated there to be little preference exhibited for either the primed or doubly primed conformations of **15** (Scheme V). Furthermore, both structures are clearly blockaded from nuclephilic attack along the direction cofacial with the dithioketal. In line with these considerations, a 1:1 mixture of **16** and **17** was obtained upon addition of the functionalized Grignard reagent derived from 2-(2-bromomethyl)-1,3-dioxane.[33] These diastereomers were readily separated chromatographically, and both were ultimately carried forward since our long-range goal was to prepare isomers of **1** as well.

The critical lactone ring was elaborated by sequential acid hydrolysis[34] and Jones oxidation[35] of **16**. Intermediate lactol **18** was not purified due to its lability toward silica gel. As a direct consequence of the coproduction of 1,3-propanediol in this reaction, excess Jones reagent was required to obtain **19** most efficaciously. Although the dithioketal protecting group was concomitantly removed while progressing from **16** to **18**, advance to **20** was easily managed.

Arrival at the first relay point, viz., (−)-**3**, required that a geminal dialkylation be performed α to the lactone carbonyl, with proper stereodisposition of the methyl and vinyl groups. Given the sizeable controlling influence anticipated to be exerted by the large substituent already present on the lactone ring in **20**, the methyl group unquestionably had to be introduced last. Consequently, the lithium enolate of **20** was initially condensed with acetaldehyde and the resulting aldol was dehydrated by β

(28) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781.

(29) For the work to follow, the dextrorotatory enriched material was diluted with racemic **12** to provide material of 46% ee. For convenience, the rotations reported for the optically active compounds leading to the first relay intermediate and beyond are extrapolated to 100% ee on the likely assumption that no optical activity is lost. The $[\alpha]^{25}_D$ established in this manner for the enantiomers of **12** is 38.6°. The actual measured values have been tabulated elsewhere (pp 59–60 of ref 30). Recrystallization was performed only on those small quantities intended for analysis so as not to achieve adventitious optical enrichment.

(30) Those interested in the entire panorama of experiments are directed to: Wiedeman, P. E., Ph.D. Thesis, The Ohio State University, 1985.

(31) (a) Collins, J. C.; Hess, W. W. *Org. Synth.* **1972**, *52*, 5. (b) Ratcliffe, R.; Rodehurst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(32) Other chromium-based oxidizing agents gave consistently lower yields, while the Corey and Swern procedures led to significant decomposition.

(33) Stowell, J. C.; Keith, D. R.; King, B. T. *Org. Synth.* **1984**, *62*, 140.

(34) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599.

(35) Paquette, L. A.; Schostarez, H.; Annis, G. D. *J. Am. Chem. Soc.* **1981**, *103*, 6526.

elimination of its mesylate derivative[36] (Scheme VI). The *E* configuration about the double bond in the ethylidene lactone **21** has been assigned following comparison of its vinyl methyl chemical shift (δ 1.83) to those reported for the (*E*)- and (*Z*)-α-ethylidene-γ-valerolactones.[37a] In this pair of model compounds, the vinyl methyl of the *Z* isomer is held in the deshielding region of the carbonyl group and appears at δ 2.09, while that of the *E* isomer does not come under this influence and appears at δ 1.82.

Deconjugative methylation of **21** proceeded with facial selectivity to provide (−)-**3** as the major product. *This compound proved identical in all respects with the degradation product obtained above, thereby enabling assignment of absolute configuration to all precursor intermediates.*[37b]

Tricyclic Lactones of Unnatural Configuration. Despite extensive degradation studies on pleuromutilin (**1a**), methods for altering the stereochemistry intrinsic to C-12 and C-14 have not been described. In expectation of a future breakthrough in the successful reconstruction of **1a** from (−)-**3**, we considered that stereoisomers **23**, **26**, and **27** (Scheme VII) might serve well as potential precursors to unnatural pleuromutilin analogues. A broader spectrum of substrates would thereby become available for the intercorrelation of structure and antibiotic activity.

Inversion of stereochemistry at the quaternary carbon α to the lactone carbonyl began by alkylation of the lithium enolate of (±)-**20** with methyl iodide. Epimerically pure (±)-**22** was formed exclusively. Introduction of the vinyl group was accomplished by subsequent condensation with (phenylseleno)acetaldehyde[38] under the conditions developed by Clive[39] and by Kowalski.[40] This protocol was selected over alternative vinyl cation synthons[41] because of the relatively mild conditions involved and their anticipated compatibility with existing functionality. Following treatment of lithiated (±)-**22** with this reagent, elimination within the resulting aldol was accomplished with methanesulfonyl chloride and triethylamine.

With the synthesis of (±)-**23** achieved, our experience with this reagent combination was extended to lactone (±)-**24**, which was comparably found to deliver (±)-**26** in stereochemically homogeneous condition. To complete this phase of the study, both enantiomers of **24** were also converted into (+)-**27** and (−)-**27** by an extension of the methodology detailed in Scheme VI for the crafting of **3** from **20**.

In summary, pleuromutilin and tiamulin have been degraded in only four steps to levorotatory lactone **3**. This important relay intermediate has been synthesized de novo. The successful route has been deployed as well for the stereoselective elaboration of (±)-**23**, (±)-**26**, and (+)- or (−)-**27**, stereoisomers of (−)-**3** that could serve as precursors to unnatural pleuromutilins epimeric at sites believed to be central to antibiotic activity.

Experimental Section[29,42]

(+)-Pleuromutilin (1a). Pleuromutilin, obtained as a crude fermentation product, was purified by chromatography (silica gel; 50% ethyl acetate in methylene chloride). Subsequent recrystallization from methylene chloride allowed isolation of the pure material as colorless crystals: mp 165–166 °C (lit.[11f] mp 165–166 °C); $[\alpha]^{22}_D$ +34.7° (*c* 1.03, $CHCl_3$) (lit.[11f] $[\alpha]^{25}_D$ +33.9° (*c* 1.00, $CHCl_3$)); IR (Nujol, cm^{-1}) 3480, 3380, 2900, 1730, 1450, 1370, 1225, 1210, 1150, 1090, 1025, 1005, 990, 960, 925, 905; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 18, 11 Hz, 1 H), 5.84 (d, *J* = 9 Hz, 1 H), 5.36 (dd, *J* = 11, 2 Hz, 1 H), 5.22 (dd, *J* = 18, 2 Hz, 1 H), 4.11–3.96 (m, 2 H), 3.37 (br s, 1 H), 2.61–2.03 (series of m, 5 H), 1.83–1.08 (series of m, 10 H), 1.43 (s, 3 H), 1.17 (s, 3 H), 0.89 (d, *J* = 8 Hz, 3 H), 0.71 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 216.83, 172.17, 139.03, 117.24, 74.64, 69.79, 61.35, 58.14, 45.45, 44.85, 44.06, 41.87, 36.65, 36.11, 34.47, 30.46, 26.88, 26.46, 24.88, 16.57, 14.81, 11.47 ppm; MS (FAB), (M^+) *m/z* 378.

Tiamulin (1b). Tiamulin was obtained quantitatively from tiamulin hydrogen fumarate by dissolving the salt into 10% sodium hydroxide solution and extracting with methylene chloride. The combined organic phases were dried and freed of solvent to provide tiamulin as a light brown oil: IR (neat, cm^{-1}) 3540, 2920, 1715, 1445, 1400, 1370, 1270, 1105, 1000, 970, 720; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (dd, *J* = 11.0, 17.4 Hz, 1 H), 5.68 (dd, *J* = 8.3 Hz, 1 H), 5.26 (dd, *J* = 1.1, 11.0 Hz, 1 H), 5.13 (dd, *J* = 1.2, 17.4 Hz, 1 H), 3.31 (m, 1 H), 3.10 (s, 2 H), 2.64–2.58 (m, 4 H), 2.46 (q, *J* = 7.1 Hz, 4 H), 2.33–2.24 (m, 2 H), 2.19–2.11 (m, 2 H), 2.08–1.98 (m, 2 H), 1.74–1.48 (m, 5 H), 1.45–1.25 (m, 2 H), 1.39 (s, 3 H), 1.19–1.01 (m, 1 H), 1.10 (s, 3 H), 0.95 (t, *J* = 7.1 Hz, 6 H), 0.82 (d, *J* = 7.0 Hz, 3 H), 0.68 (d, *J* = 6.6 Hz, 3 H).

(−)-Pleuromutilone (2a). Pleuromutilin (**1a**) (5.00 g, 13.2 mmol) was dissolved in methylene chloride (200 mL) and pyridinium chlorochromate (4.2 g, 19 mmol) was added. The mixture was stirred overnight at room temperature. Ether (300 mL) was added, and the mixture was stirred to obtain homogeneity. Passage through a short column (Florisil; ether elution) gave crude **2a** after solvent evaporation. Crystallization from methylene chloride furnished pure pleuromutilone (4.28 g, 86%) as colorless crystals: mp 178.0–179.5 °C (lit.[11d] mp 178–179 °C); $[\alpha]^{21}_D$ −8.2° (*c* 2.45, $CHCl_3$) (lit.[11c] $[\alpha]^{20}_D$ −8° (*c* 1.038, $CHCl_3$)); IR (Nujol, cm^{-1}) 3480, 2900, 1730, 1695, 1455, 1370, 1270, 1230, 1205, 1150, 1080, 1070, 1050, 985, 970, 945, 920, 905; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (dd, *J* = 178 10 Hz, 1 H), 6.03 (d, *J* = 8 Hz, 1 H), 5.36 (d, *J* = 10 Hz, 1 H), 5.07 (d, *J* = 17 Hz, 1 H), 4.23–4.03 (m, 2 H), 3.34–3.25 (m, 1 H), 2.50–2.02 (series of m, 4 H), 1.73–1.16 (series of m, 9 H), 1.48 (s, 3 H), 1.16 (s, 3 H), 1.10 (d, *J* = 6 Hz, 3 H), 0.76 (d, *J* = 5 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 188.47, 186.82, 153.37, 127.49, 110.16, 79.33, 72.05, 64.52, 62.63, 58.26, 51.90, 51.66, 50.39, 49.08, 45.10, 43.16, 39.32, 36.90, 35.20, 28.89, 27.33, 26.46 ppm; MS (FAB), ($M^+ - 1$) *m/z* 375.

Tiamulone (2b). Tiamulin hydrogen fumarate (5.00 g, 8.20 mmol) was dissolved in 10% sodium hydroxide solution (100 mL). This solution was extracted with methylene chloride (4 × 50 mL). The combined organic phases were dried and filtered. Pyridinium chlorochromate (6.00 g, 27.8 mmol) was added, and the reaction mixture was stirred at room temperature overnight, extracted sequentially with 10% potassium hydroxide solution (2 × 250 mL), water (250 mL), and brine (2 × 100 mL), dried, and freed of solvent.

Chromium salts were removed by passage of the residue through a short chromatography column (silica gel; methanol elution). A second chromatography (silica gel; elution with 5% methanol in methylene chloride) furnished **2b** (3.90 g, 97%) as a pale yellow oil: IR (neat, cm^{-1}) 2970, 2940, 2810, 1730, 1700, 1620, 1455, 1415, 1375, 1330, 1280, 1200, 1150, 1115, 1095, 1060, 1000, 990, 965, 925, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 17.6, 10.8 Hz, 1 H), 5.87–5.77 (m, 1 H), 5.18 (d, *J* = 10.7 Hz, 1 H), 4.90 (d, *J* = 17.5 Hz, 1 H), 3.11 (br s, 2 H), 3.05–2.75 (series of m, 2 H), 2.64–2.51 (m, 4 H), 2.41 (q, *J* = 7.1 Hz, 4 H), 2.18–1.97 (m, 3 H), 1.91 (dd, *J* = 15.6, 8.5 Hz, 1 H), 1.54–1.25 (series of m, 7 H), 1.34 (s, 3 H), 0.99 (s, 3 H), 0.92 (t, *J* = 7.4 Hz, 6 H), 0.88 (d, *J* = 7.1

(36) (a) Narasaka, K.; Uchimura, T. *Chem. Lett.* **1982**, *57*. (b) Torii, S.; Okamoto, T.; Kadono, S. *Ibid.* **1977**, 495.

(37) (a) Yamamoto, K.; Tomo, Y. *Chem. Lett.* **1983**, 531. (b) The optical rotation of (−)-**3** was −10.0°, which is 3.1° more negative than the value observed (−6.9°) for (−)-**3** obtained by degradation. The discrepancy likely arises from small weighing errors and the unusually labile nature of the dithioketal to hydrolysis. A small (<3%) but unequal amount of enone could have been present in either sample to alter the observed rotation. The identification of (−)-**3** is strengthened by the independent synthesis of (+)-**3**[30] and two other possible diastereomers.

(38) Baudat, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1406.

(39) (a) Clive, D. L. J.; Russell, C. G.; Suresh, C. S. *J. Org. Chem.* **1982**, *47*, 1632. (b) Clive, D. L. J.; Russell, C. G. *J. Chem. Soc., Chem. Commun.* **1981**, 434.

(40) Kowalski, C. J.; Dung, J.-S. *J. Am. Chem. Soc.* **1980**, *102*, 7950.

(41) (a) Ohnuma, T.; Hata, N.; Fujiwara, H.; Ban, Y. *J. Org. Chem.* **1982**, *47*, 4713. (b) Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251. (c) Koppel, G. A.; Kinnick, M. D. *J. Chem. Soc., Chem. Commun.* **1975**, 473.

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

Hz, 3 H), 0.64 (d, J = 5.8 Hz, 3 H).

(6*R*,7*R*)-7-[(2*R*,4*S*)-5-Ethyltetrahydro-5-hydroxy-4-methyl-4-vinyl-2-furyl]-4,5,6,7-tetrahydro-6,7-dimethyl-1-indanone (5). Pleuromutilone (**2a**) (500 mg, 1.33 mmol) was dissolved in a 10% solution of potassium hydroxide in ethanol (50 mL), and the solution was heated at reflux overnight. After being cooled, the solution was poured into water (100 mL), acidified with concentrated hydrochloric acid, and extracted with dichloromethane (3 × 75 mL). The combined organic phases were extracted with saturated sodium bicarbonate solution, dried, and freed of solvent. Purification was achieved by column chromatography (Florisil; elution with 10% ethyl acetate in methylene chloride) to afford **5** (351 mg, 83%) as a pale yellow oil: IR (neat, cm^{-1}) 3450, 2950, 1730, 1680, 1620, 1450, 1410, 1370, 1275, 1230, 1185, 1115, 990, 965, 900; ^1H NMR (300 MHz, $CDCl_3$) δ 6.1–5.8 (m, 1 H), 5.1–4.9 (m, 2 H), 4.6 and 4.1 (m, 1 H), 2.6–0.9 (series of m, 26 H).

(−)-(3*S*,5*R*)-Dihydro-3-methyl-5-[(4*R*,5*R*)-4,5,6,7-tetrahydro-4,5-dimethyl-3-oxo-4-indanyl]-3-vinyl-2(3*H*)-furanone (6). Pleuromutilone (**2a**) (3.00 g, 7.98 mmol) was treated with a 10% solution of potassium hydroxide in ethanol (300 mL) at the reflux temperature overnight. After being cooled, the solution was poured into water (600 mL), acidified with concentrated hydrochloric acid, and extracted with methylene chloride (3 × 500 mL). The combined organic phases were washed with saturated sodium bicarbonate solution, dried, and freed of solvent. The crude hemiacetal **5**, a yellow oil, was immediately dissolved in methylene chloride (150 mL). Pyridinium chlorochromate (10 g, 46 mmol) was added, and the mixture was stirred overnight at room temperature. Ether (600 mL) was added, and the mixture was passed through a short column (Florisil; ether elution). After concentration in vacuo, the crude material was subjected to a second chromatography (silica gel; elution with 30% ethyl acetate in petroleum ether) to afford lactone **6** (1.42 g, 60%) as a colorless solid: mp 123–124 °C; $[\alpha]^{24}_D$ −16.9° (c 1.54, $CHCl_3$); IR (Nujol, cm^{-1}) 2900, 1760, 1680, 1630, 1455, 1375, 1295, 1280, 1190, 1180, 1115, 1085, 1045, 1010, 985, 925; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (dd, J = 17, 9 Hz, 1 H), 5.15 (d, J = 17 Hz, 1 H), 5.14 (d, J = 9 Hz, 1 H), 5.02 (dd, J = 10, 5 Hz, 1 H), 2.50–2.15 (series of m, 10 H), 1.84–1.74 (m, 1 H), 1.30 (s, 3 H), 1.22 (s, 3 H), 0.96 (d, J = 5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 208.16, 179.54, 175.53, 140.31, 140.05, 114.71, 78.93, 46.37, 40.47, 38.21, 36.43, 35.21, 29.41, 27.38, 26.90, 23.02, 19.00, 16.75 ppm.

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.66; H, 8.32.

(−)-(3*S*,5*R*)-Dihydro-3-methyl-5-[(6′*R*,7′*R*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-3-vinyl-2(3*H*)-furanone (3). Lactone **6** (100 mg, 0.347 mmol) was dissolved in benzene (25 mL) along with a catalytic amount of p-toluenesulfonic acid (10 mg). Ethanedithiol (0.20 mL, 2.38 mmol) was added, and the mixture was heated at reflux overnight in a Dean–Stark apparatus. After 24 h, additional ethanedithiol (0.10 mL) was added. No starting material remained after a total of 50 h. The reaction mixture was cooled, poured into benzene (50 mL), extracted with 10% sodium hydroxide solution and water, dried, and freed of solvent. The residue was purified chromatographically (silica gel; methylene chloride elution) to yield thioacetal **3** (98 mg, 78%) as a colorless oil, which slowly crystallized as an off-white solid upon cooling: mp 75–76 °C; $[\alpha]^{25}_D$ −16.3° (CH_2Cl_2), $[\alpha]^{25}_D$ −6.9° (c 2.07, $CHCl_3$); IR (neat, cm^{-1}) 2960, 2920, 2870, 2830, 1765, 1640, 1450, 1420, 1370, 1330, 1265, 1190, 1090, 915, 845, 810, 730, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (dd, J = 17.5, 10.5 Hz, 1 H), 5.20 (d, J = 16.7 Hz, 1 H), 5.20 (d, J = 11.3 Hz, 1 H), 4.85 (dd, J = 11.1, 5.8 Hz, 1 H), 3.37–3.12 (series of m, 4 H), 2.61 (t, J = 12.0 Hz, 1 H), 2.47–2.09 (series of m, 6 H), 1.89 (dd, J = 12.6, 5.7 Hz, 1 H), 1.75–1.43 (series of m, 3 H), 1.52 (s, 3 H), 1.36 (s, 3 H), 1.04 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 179.36, 145.01, 140.03, 136.09, 114.42, 80.14, 77.53, 49.00, 46.46, 42.81, 41.06, 40.02, 38.45, 33.77, 27.10, 25.94 (2 C), 22.49, 19.88, 16.66 ppm; MS, calcd (M^+) m/z 364.1531, obsd 364.1538.

Anal. Calcd for $C_{20}H_{28}O_2S_2$: C, 65.89; H, 7.74. Found: C, 65.71; H, 7.80.

Ethyl (1*RS*,2*RS*)-1,2-Dimethyl-6-oxocyclohexanecarboxylate (8). To a suspension of sodium hydride (2.60 g, 0.108 mol) in dry dimethylformamide (450 mL) was slowly added β-keto ester **7** (20.0 g, 0.108 mol). After hydrogen evolution had ceased, methyl iodide (33.9 g, 0.239 mol) was introduced. The reaction mixture was heated at 60 °C with stirring for 72 h, at which time GC analysis (6 ft, 5% SE 30, 150 °C) showed a mixture of the desired trans isomer, the cis isomer, and polyalkylated material to be present in a ratio of 80.5:12:7.5, respectively. The reaction mixture was worked up in three batches, with each initially partitioned between ether (400 mL) and water (400 mL). The aqueous layers were extracted with ether (2 × 200 mL). The combined organic phases were then back-washed with water (3 × 100 mL) prior to drying. After removal of solvent, the products were separated by spinning-band distillation, bp 97.5–104.0 °C (7–10 mm). The fractions containing 90% or more of the desired trans isomer **8** (10.0 g, 47%), a colorless oil, were taken on while the remainder was recycled: IR (neat, cm^{-1}) 2940, 1740, 1715, 1448, 1372, 1245, 1230, 1196, 1020, 944; ^1H NMR (90 MHz, $CDCl_3$) δ 4.11 (q, J = 7 Hz, 2 H), 3.00–1.45 (series of m, 7 H), 1.31 (s, 3 H), 1.24 (t, J = 6 Hz, 3 H), 1.13 (d, J = 6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 208.45, 171.37, 60.93, 43.81, 39.87, 30.34, 25.48, 21.11, 18.87, 17.05, 14.20 ppm; MS, calcd (M^+) m/z 198.1256, obsd 198.1260.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.59; H, 9.15.

Ethyl (1*RS*,6*RS*)-2-Hydroxy-1,6-dimethyl-2-[3-[[tetrahydro-2*H*-pyran-2-yl]oxy]-1-propynyl]cyclohexanecarboxylate (9a). To a mixture of ether (60 mL), tetrahydrofuran (20 mL), and ethylmagnesium bromide (38 mL, 1.0 M in ether) was slowly added from a syringe at room temperature tetrahydro-2-(2-propynyloxy)-2H-pyran (5.30 g, 37.8 mmol). After ethane evolution had ceased, β-keto ester **8** (5.00 g, 25.2 mmol) was also added from a syringe. After being stirred for 15 h at room temperature, the reaction mixture had become yellow and a gray solid had precipitated. TLC analysis (25% ethyl acetate in petroleum ether) showed no starting material to remain. Ice was added, and the product was extracted into ether–petroleum ether (1:1). The organic phase was dried and evaporated. The crude product may be used as is or purified with a Waters Prep 500 HPLC (silica gel, elution with 20% ethyl acetate in petroleum ether) to give **9a** (6.09 g, 71%) as a viscous yellow oil: IR (neat, cm^{-1}) 3460, 3300, 2950, 1730, 1460, 1450, 1352, 957, 911, 880, 825; ^1H NMR (90 MHz, $CDCl_3$) δ 4.75 (br s, 1 H), 4.25 (s, 2 H), 4.15 (q, J = 6 Hz, 2 H), 3.58 (br s, 2 H), 2.50–1.38 (series of m, 14 H), 1.35 (s, 3 H), 1.27 (t, J = 6 Hz, 3 H), 0.95 (d, J = 8 Hz, 3 H); MS, calcd ($M^+ - C_5H_8O$) m/z 254.1518, obsd 254.1513.

Ethyl (1*RS*,6*RS*)-2-Hydroxy-2-(3-hydroxy-1-propynyl)-6-methylcyclohexanecarboxylate (9b). Ethanol (2 mL) and **9a** (200 mg, 1.01 mmol) were combined. After cooling to 0 °C with an ice bath, concentrated sulfuric acid (1 mL) was slowly added. The reaction mixture was stirred for 45 min followed by neutralization with saturated sodium bicarbonate solution. The aqueous mixture was extracted with ether and dried before evaporation of the solvent. The product was separated and purified by MPLC (silica gel; elution with 25% petroleum ether in ethyl acetate) to produce **9b** (128 mg, 50%) as a white solid: mp 62–63 °C; IR ($CHCl_3$, cm^{-1}) 3400, 2940, 1705, 1441, 1372, 1275, 1230, 1068, 1010; ^1H NMR (90 MHz, $CDCl_3$) δ 4.23 (s, 2 H), 4.12 (q, J = 7 Hz, 2 H), 3.10–2.80 (m, 1 H), 2.40–1.40 (series of m, 8 H), 1.45 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H), 0.97 (d, J = 7 Hz, 3 H); MS, calcd ($M^+ - H_2O$) m/z 236.1412, obsd 236.1407.

Ethyl (4*RS*,5*RS*)-4,5,6,7-Tetrahydro-4,5-dimethyl-3-oxo-4-indancarboxylate (10). A solution of **9a** (996 mg, 2.94 mmol) in ethanol (2 mL) was cooled in an ice bath to 0 °C, and concentrated sulfuric acid (3 mL) was added slowly dropwise with resultant exotherm and color change to dark brown. After 4.5 h, the reaction mixture was neutralized with saturated sodium bicarbonate solution, extracted with ether, and dried. After solvent removal under vacuum, the crude product was purified by HPLC (silica gel; elution with 25% petroleum ether in ethyl acetate) to yield **10** (406 mg, 59%) as a yellow oil: IR (neat, cm^{-1}) 2930, 1730, 1700, 1645, 1445, 1380, 1300, 1032, 975; ^1H NMR (90 MHz, $CDCl_3$) δ 4.10 (q, J = 7 Hz, 2 H), 2.67–2.00 (m, 6 H), 1.90–1.50 (m, 3 H), 1.45 (s, 3 H), 1.20 (t, J = 7 Hz, 3 H), 0.95 (d, J = 6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 207.00, 173.62, 172.95, 141.10, 60.50, 45.45, 39.20, 34.77, 29.74, 27.79, 27.19, 21.36, 16.08, 14.32 ppm; MS, calcd (M^+) m/z 236.1412, obsd 236.1427.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.90; H, 8.67.

Ethyl (6′*RS*,7′*RS*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-carboxylate (11). A solution of enone **10** (9.99 g, 42.3 mmol) in benzene (200 mL) was treated with 1,2-ethanedithiol (50 mL, 0.60 mol) and *p*-toluenesulfonic acid monohydrate (1.0 g) and brought to the reflux temperature. After overnight heating, TLC analysis (20% ethyl acetate in petroleum ether) showed the reaction to be complete. The reaction mixture was diluted with chloroform (250 mL) and extracted with 1 N sodium hydroxide solution (4 × 500 mL) followed by drying and solvent evaporation. The product was purified chromatographically (silica gel; elution with 10% ethyl acetate in petroleum ether) to give **11** (12.92 g, 98%) as a light brown solid: mp 70–73 °C; IR (neat, cm^{-1}) 2920, 1725, 1445, 1368, 1221, 1181, 1105, 1035, 900, 809, 724; ^1H NMR (90 MHz, $CDCl_3$) δ 4.08 (q, J = 7 Hz, 2 H), 3.47–2.67 (m, 4 H), 2.40 (br s, 2 H), 2.33–1.90 (m, 4 H), 1.80–1.37 (m, 3 H), 1.50 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H), 0.91 (d, J = 6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 173.95, 143.22, 134.48, 75.88, 59.28, 49.42, 47.04, 39.61 (2 C), 37.62, 33.59, 26.70, 26.22, 21.36, 15.87, 13.35 ppm; MS, calcd (M^+) m/z 312.1218, obsd 312.1225.

(6′*RS*,7′*RS*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-methanol (12). Diisobutylaluminum hydride (265 mL, 0.265 mol, 1 N in hexane) was slowly added via syringe to a solution of **11** (27.65 g, 88.5 mmol) in toluene (100 mL). After 3 h of stirring at room temperature, TLC analysis (20% ethyl acetate in petroleum ether) showed the conversion to be complete. The reaction mixture was quenched with methanol–water (1:1). The gelatinous aluminum salts were dissolved with a minimum of 10% hydrochloric acid solution. The layers were separated, and the aqueous phase was further extracted with ether. The organic phases were combined, dried, and concentrated in vacuo. The product was purified with a Waters Prep 500 HPLC (silica gel, elution with 10% ethyl acetate in petroleum ether) to furnish **12** (22.17 g, 93%) as a white solid: mp 47–50 °C; IR (neat, cm^{-1}) 3460, 2935, 1630, 1420, 1365, 1270, 1018, 808, 728; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (AB q, J = 11.6 Hz, $\Delta\nu$ = 35 Hz, 2 H), 3.35–3.28 (m, 4 H), 2.45–2.29 (m, 4 H), 2.06–2.01 (m, 3 H), 1.70–1.65 (m, 3 H), 1.27 (s, 3 H), 1.00 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 144.77, 136.42, 77.43, 65.78, 49.37, 42.38, 39.81, 39.42, 39.28, 33.93, 27.53, 26.02, 23.55, 15.39 ppm; MS, calcd (M^+) m/z 270.1112, obsd 270.1119.

(+)-[(6′*R*,7′*R*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]methyl [(α*R*)-α-Methylbenzyl]carbamate (13) and (+)-[(6′*S*,7′*S*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]methyl [(α*R*)-α-Methylbenzyl]carbamate (14). In a 250-mL three-necked flask equipped with a gas inlet tube and condenser topped with a gas inlet adapter were combined dry toluene (130 mL) and (*R*)-(+)-α-methylbenzylamine (2.86 mL, 22.2 mmol). Hydrogen chloride was passed through the gas inlet tube above the surface of the solvent resulting in precipitation of the hydrochloride salt. When no further precipitation was observed, the tube was lowered beneath the solvent surface to ensure complete transformation of the amine to the corresponding salt. The gas inlet adapter was connected to a trap containing 20% aqueous sodium hydroxide, and phosgene was bubbled through the reaction mixture after first going through traps of cottonseed oil and sulfuric acid. The mixture was brought to the reflux temperature and exposure to phosgene was continued for 40 min after the disappearance of all of the precipitate. Subsequently, the solution was flushed with nitrogen for 1 h to remove residual phosgene. Alcohol **12** (2.00 g, 7.39 mmol) dissolved in a minimum quantity of toluene containing 4-(dimethylamino)pyridine (200 mg) was then introduced. The reaction mixture was kept at the reflux temperature, and the progress of carbamate formation was monitored by TLC analysis (10% ethyl acetate in petroleum ether). Reaction was complete after 48 h, at which point the solution was cooled, diluted with ether, and extracted with saturated sodium bicarbonate solution and brine before being dried and freed of solvent. The diastereomers were separated by HPLC (Waters Prep 500; silica gel; elution with 20% ethyl acetate in petroleum ether) employing recycling and band-shaving techniques: overall yield 2.69 g (87%); faster eluting diastereomer **14**, 877 mg (28%); slower eluting diastereomer **13**, 860 mg (28%); recovered mixture, 951 mg (31%).

For **13**: $[\alpha]^{25}_D$ +28.8° (*c* 1.72, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3450, 2960, 2935, 1710, 1500, 1448, 1408, 1371, 1330, 1278, 1221, 1055; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5 H), 4.89 (br s, 1 H), 4.50 (AB q, J = 10.7 Hz, $\Delta\nu$ = 26 Hz, 2 H), 3.35–3.15 (m, 4 H), 2.35–1.22 (series of m, 10 H), 1.47 (d, J = 6.5 Hz, 3 H), 1.36 (s, 3 H), 0.91 (d, J = 5.1 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 156.09, 142.14, 136.14, 130.83, 128.60, 127.19, 125.85, 76.73, 67.85, 50.86, 49.51, 40.57, 40.12, 39.17, 36.55, 33.93, 25.88, 24.47 (2 C), 22.75, 14.96 ppm; MS, calcd (M^+) m/z 417.1796, obsd 417.1821.

For **14**: $[\alpha]^{25}_D$ +13.1° (*c* 1.96, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3450, 2962, 2930, 1710, 1500, 1448, 1408, 1371, 1330, 1278, 1221, 1055; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5 H), 4.86 (br s, 1 H), 4.51 (AB q, J = 10.8 Hz, $\Delta\nu$ = 31 Hz, 2 H), 3.35–3.16 (m, 4 H), 2.38–1.96 (series of m, 5 H), 1.86–1.20 (series of m, 8 H), 1.48 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 156.19, 144.06, 142.20, 136.14, 128.60, 127.19, 125.85, 76.73, 67.78, 50.79, 49.51, 40.57, 40.06, 39.23, 36.74, 33.92, 26.00, 24.60, 24.28, 22.75, 15.08 ppm; MS, calcd (M^+) m/z 417.1796, obsd 417.1821.

(+)-(6′*R*,7′*R*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-methanol and (−)-(6′*S*,7′*S*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-methanol (12). Carbamate **14** (200 mg, 0.47 mmol) was dissolved in toluene (10 mL) containing triethylamine (0.14 mL, 1.0 mmol). As the reaction mixture was brought to reflux, trichlorosilane (0.10 mL, 1.0 mmol) dissolved in toluene (2 mL) was added dropwise over several minutes. After 6 h at the reflux temperature, TLC analysis (15% ethyl acetate in petroleum ether) showed the reaction to be complete. The reaction mixture was cooled, diluted with ether (40 mL), washed with saturated ammonium chloride solution (2 × 20 mL), and dried before removal of solvent in vacuo. The product was purified by MPLC (silica gel; elution with 15% ethyl acetate in petroleum ether) to afford (−)-**12** (88 mg, 68%), $[\alpha]^{25}_D$ −38.9° (*c* 4.78, $CHCl_3$).

Diastereomer **13** (200 mg, 0.479 mmol) was treated identically producing the enantiomeric alcohol (+)-**12** (80 mg, 62%), $[\alpha]^{25}_D$ +38.3° (*c* 4.86, $CHCl_3$). The spectral data for the individual enantiomers were identical with those of racemic **12**.

Neither enantiomer was obtained optically pure by this procedure. The extent of purity was determined by a ^1H NMR study employing tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) as the shift reagent. The shift reagent was added in small aliquots up to a total of 80 molar percent. In both cases, those spectra obtained from the samples containing 15 molar percent [Eu(hfc)$_3$] were best suited for determining relative peak areas of enantiomer with a planimeter. The peak chosen for study was the methyl singlet. In a subsequent larger scale experiment from that described above, cleavage of a carbamate mixture enriched in **14** produced an enantiomeric mixture enriched with the levorotatory enantiomer. The ratio of the two enantiomers was 77.9 to 22.1 or 56% ee, and this mixture exhibited $[\alpha]^{25}_D$ −21.8° (*c* 4.78, $CHCl_3$). A sample enriched in the dextrorotatory alcohol in a ratio of 89.1 to 10.9 or 78% ee exhibited $[\alpha]^{25}_D$ +29.4° (*c* 4.86, $CHCl_3$). There was insufficient quantity of the dextrorotatory material to continue the synthetic sequence. Consequently, the substance was further diluted with racemic alcohol to provide material of 46% ee, $[\alpha]^{25}_D$ +17.4° (*c* 5.07, $CHCl_3$). For the sake of clarity, the optical rotations reported above and for the compounds that follow have been extrapolated to optical purity.

(+)-(6′*R*,7′*R*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-carboxaldehyde and (−)-(6′*S*,7′*S*)-4′,5′,6′,7′-Tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-carboxaldehyde (15). Chromium trioxide (20.43 g, 0.204 mol, dried over P_2O_5 at 100 °C (0.5 mm)) was slowly added to dry methylene chloride (140 mL) and pyridine (33.0 mL, 4.09 mol). The Collins reagent was permitted to form over 20 min. The addition tube was replaced with an addition funnel, and (−)-**12** (5.53 g, 20.4 mmol) dissolved in methylene chloride (2 mL) was added dropwise. Stirring was continued for 45 min. The reaction mixture was diluted with ether (1600 mL) and extracted in turn with 5% sodium hydroxide solution (3 × 1000 mL), 5% hydrochloric acid solution (2 × 1000 mL), 5% sodium bicarbonate solution (2 × 1000 mL), and brine (1000 mL). The organic layer was dried, and the solvent was removed under vacuum. Chromatographic purification on silica gel (elution with 10% ethyl acetate in petroleum ether) afforded (−)-**15** (4.41 g,

80%) as a white solid: mp 103–104 °C; $[\alpha]^{25}_D$ −111.7° (c 6.49, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2960, 2750, 1729, 1445, 1335, 1292, 828; ^1H NMR (90 MHz, $CDCl_3$) δ 9.79 (s, 1 H), 3.37–3.00 (m, 4 H), 2.57–2.03 (m, 6 H), 1.80–1.53 (m, 3 H), 1.47 (s, 3 H), 0.97 (d, J = 6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 206.70, 145.65, 134.97, 77.07, 51.58, 49.52, 40.66 (2 C), 39.32, 34.53, 27.79, 26.40, 20.15, 15.78 ppm; MS, calcd (M^+) m/z 268.0956, obsd 268.0963.

Anal. Calcd for $C_{14}H_{20}OS_2$: C, 62.64; H, 7.51. Found: C, 62.57; H, 7.55.

Comparable oxidation of (+)-**12** (6.22 g, 23.0 mmol) yielded (+)-**15** (3.79 g, 61%), $[\alpha]^{25}_D$ +111.3°.

The Four Diastereomeric α-(2-*m*-Dioxan-2-ylethyl)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-methanols (16 and 17). A few iodine crystals, magnesium turnings (952 mg, 39.2 mmol), and tetrahydrofuran (18 mL) were mixed. 2-(2-Bromoethyl)-1,3-dioxane (6.37 g, 32.6 mmol) dissolved in tetrahydrofuran (12 mL) was added dropwise. Reflux began spontaneously and heating was continued for an additional hour. During this period, 24 mL of tetrahydrofuran was introduced at a rate that did not interrupt the reflux. After an additional 1.5 h, (+)-**15** (1.75 g, 6.53 mmol) dissolved in a minimum quantity of tetrahydrofuran was added. Heating was continued overnight. After 10 h, TLC analysis (10% ethyl acetate in petroleum ether) indicated the reaction to be complete. The cooled reaction mixture was quenched with saturated ammonium chloride solution, followed by 10% hydrochloric acid to dissolve the magnesium salts. The product was extracted into ether, dried, and freed of solvent. Separation of the diastereomers was performed with a Waters Prep 500 HPLC (silica gel; elution with 25% ethyl acetate in petroleum ether): overall yield, 2.30 g (92%). The faster eluting diastereomer **16** was isolated as a light yellow oil (1.17 g, 47%); $[\alpha]^{25}_D$ −0.5° (c 10.6, $CHCl_3$). The slower eluting diastereomer **17** was obtained as a white solid (1.13 g, 45%), mp 116–120 °C; $[\alpha]^{25}_D$ +8.5° (c 12.0, $CHCl_3$).

For **16**: IR ($CDCl_3$, cm^{-1}) 3420, 2960, 1425, 1250, 1140, 995; ^1H NMR (90 MHz, $CDCl_3$) δ 4.64 (t, J = 5 Hz, 1 H), 4.43–3.53 (series of m, 5 H), 3.38 (br s, 4 H), 2.73–1.23 (series of m, 16 H), 1.40 (s, 3 H), 1.13 (d, J = 7 Hz, 3 H); ^{13}C NMR (20 MHz, CCl_4) 143.76, 140.18, 103.29, 77.98, 75.13, 67.30 (2 C), 50.91, 46.42, 40.54, 39.02, 34.71, 33.98, 30.77, 29.80, 28.82, 27.85, 26.76, 25.12, 17.72 ppm; MS, calcd ($M^+ - C_3H_7O_2$) m/z 309.1347, obsd 309.1325.

For **17**: IR ($CDCl_3$, cm^{-1}) 3460, 2960, 1425, 1250, 1140, 1075; ^1H NMR (90 MHz, $CDCl_3$) δ 4.59 (t, J = 5 Hz, 1 H), 4.14–3.65 (series of m, 5 H), 3.35–3.25 (m, 4 H), 2.46–1.43 (series of m, 16 H), 1.38 (s, 3 H), 0.96 (d, J = 7 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 160.98, 152.42, 108.79, 78.62, 73.16, 64.24 (2 C), 42.33, 37.42, 30.80, 29.89, 29.28, 24.61, 23.28, 21.58, 14.96, 14.11, 13.02, 10.53, 7.50 ppm; MS, calcd ($M^+ - C_3H_8O_2$) m/z 308.1268, obsd 308.1319.

Analogous reactions were carried out on (−)-**15**. A sample of this aldehyde, $[\alpha]^{25}_D$ −111.7° (4.40 g, 16.4 mmol), delivered 2.88 g (46 %) of the diastereomer corresponding to **16** (i.e., **16***), whose $[\alpha]^{25}_D$ was +4.6° (c 5.6, $CHCl_3$), and 2.95 g (48%) of the diastereomer corresponding to **17** (i.e., **17***), having $[\alpha]^{25}_D$ +16.2° (c 5.65, $CHCl_3$).

Hydrolysis–Oxidation of the Diastereomeric Hydroxy Acetals 16 and 17. General Procedure. A 4.15 g (10.8 mmol) sample of **17*** exhibiting $[\alpha]^{25}_D$ +16.2° was combined with *p*-toluenesulfonic acid monohydrate (400 mg), acetone (100 mL), and water (50 mL). The mixture was heated overnight at the reflux temperature. TLC analysis (50% ethyl acetate in petroleum ether) showed the reaction to be complete. The mixture was concentrated under vacuum. The residue was diluted with water (200 mL) and washed with methylene chloride (4 × 100 mL) before being dried. The solvent was evaporated, leaving the lactol A (3.18 g) as a crude brown oil, which was used immediately in the next step due to its lability: IR (neat, cm^{-1}) 3420, 2930, 1690, 1622, 1450, 1343, 1270, 1210, 1170, 1060, 808, 732.

Entirely comparable treatment of **17** (3.03 g, 7.88 mmol) produced 2.50 g of lactol B.

From 2.88 g (7.49 mmol) of **16***, $[\alpha]^{25}_D$ +4.6°, there was isolated 2.22 g of lactol C: IR (neat, cm^{-1}) 3430, 2930, 1690, 1620, 1380, 1285, 1030, 980, 730.

Analogous hydrolysis of **16**, $[\alpha]^{25}_D$ −0.5°, gave 2.34 g of **18**.

Crude lactol A (3.18 g) was dissolved in acetone (125 mL) and cooled to approximately 4 °C in an ice bath. The reaction mixture was titrated with Jones reagent until an orange color persisted, quenched with water, extracted with ether, and dried. After removal of the solvent under vacuum, the lactone was purified with the aid of a Chromatotron (silica gel; 4-mm plate; elution with 50% ethyl acetate in petroleum ether) to afford (−)-keto lactone (1.82 g, 58% from **17***) as a colorless oil, $[\alpha]^{25}_D$ −37.5° (c 6.63, $CHCl_3$).

A second keto lactone (1.11 g, 45%) $[\alpha]^{25}_D$ +38.3° (c 6.01, $CHCl_3$), was produced analogously from lactol B (2.50 g): IR ($CHCl_3$, cm^{-1}) 2970, 1770, 1690, 1624, 1460, 1380, 1285, 1168, 972, 905; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (dd, J = 8.6, 6.9 Hz, 1 H), 2.68–1.97 (series of m, 10 H), 1.60–1.41 (m, 3 H), 1.27 (s, 3 H), 1.00 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 209.27, 180.40, 177.71, 138.04, 83.30, 41.27, 40.95, 35.45, 29.70, 29.06, 28.55, 27.28, 24.78, 19.42, 15.39 ppm; MS, calcd (M^+) m/z 248.1412, obsd 248.1418.

In like fashion, the enantiomeric lactols derived from (−)-**16** (3.09 g, 8.03 mmol), $[\alpha]^{25}_D$ −0.5°, and (+)-**16** (2.88 g, 7.49 mmol), $[\alpha]^{25}_D$ +4.6°, were transformed to (−)-**19** (0.951 g, 41%), $[\alpha]^{25}_D$ −14.6° (c 5.03, $CHCl_3$), and the enantiomer of **19** (1.017 g, 46%), $[\alpha]^{25}_D$ +20.5° (c 5.72, $CHCl_3$), respectively: IR ($CHCl_3$, cm^{-1}) 2930, 1770, 1690, 1618, 1450, 1382, 1238, 1170, 990, 907; ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (t, J = 6.5 Hz, 1 H), 2.46–2.28 (m, 8 H), 2.00–1.87 (m, 2 H), 1.70–1.62 (m, 3 H), 1.22 (s, 3 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 208.44, 177.33, 176.12, 140.34, 82.53, 40.75, 38.58, 35.26, 29.45, 29.13, 27.66, 26.83, 24.21, 18.52, 16.74 ppm; MS, calcd (M^+) m/z 248.1412, obsd 248.1418.

(+)-(5*R*)-Dihydro-5-[(6′*R*,7′*R*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-2(3*H*)-furanone (20) and Its Enantiomer. A flask equipped with a Dean–Stark apparatus was charged with racemic **19** (762 mg, 3.07 mmol), benzene (45 mL), *p*-toluenesulfonic acid monohydrate (70 mg), and 1,2-ethanedithiol (3.0 mL, 37 mmol). The reaction mixture was brought to reflux and monitored daily by TLC analysis (20% ethyl acetate in petroleum ether). More ethanedithiol (1.5 mL) was added incrementally until no further progress in the reaction was observed. The reaction mixture was diluted with ether, washed several times with 1 N sodium hydroxide solution, dried, and freed of solvent. The desired product was separated from remaining starting material by MPLC (silica gel; elution with 25% ethyl acetate in petroleum ether). The recovered starting material amounted to 113 mg, while racemic **20** (479 mg, 48% or 57% based on recovered starting material) was obtained as an off-white solid: mp 105–107 °C; IR (C_6D_6, cm^{-1}) 2920, 1775, 1465, 1425, 1270, 1190, 1015, 985, 895, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (dd, J = 9.3, 6.4 Hz, 1 H), 3.38–3.12 (series of m, 4 H), 2.51–2.02 (series of m, 10 H), 1.69–1.57 (m, 3 H), 1.51 (s, 3 H), 1.02 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (20 MHz, C_6D_6) 175.80, 144.79, 137.27, 83.01, 78.04, 49.64, 43.93, 41.69, 40.23, 38.83, 34.04, 29.37, 27.36, 26.33, 26.15, 20.08, 16.74 ppm; MS, calcd (M^+) m/z 324.1218, obsd 324.1226.

Reaction of (−)-**19** (951 mg, 3.83 mmol), $[\alpha]^{25}_D$ −14.6°, produced (+)-**20** (551, mg, 44%), $[\alpha]^{25}_D$ +5.7° (c 6.76, $CHCl_3$). Correspondingly, (+)-**19** (1.017 g, 4.09 mmol), $[\alpha]^{25}_D$ +20.5°, yielded (−)-**20** (599 mg, 45%), $[\alpha]^{25}_D$ −12.0° (c 5.70, $CHCl_3$).

(+)-(5*S*)-Dihydro-5-[(6′*R*,7′*R*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1-indan]-7′-yl]-2(3*H*)-furanone (24) and Its Enantiomer. The diastereomer was first prepared in the predescribed manner from racemic keto lactone (413 mg, 1.66 mmol). The racemic product **24** was obtained as an off-white solid (464 mg, 86%): mp 99–101 °C; IR (C_6D_6, cm^{-1}) 2960, 1780, 1425, 1250, 1195, 1025, 855, 693; ^1H NMR (200 MHz, C_6D_6) δ 4.52 (dd, J = 8.3, 7.1 Hz, 1 H), 2.99–2.72 (m, 4 H), 2.41–1.37 (series of m, 13 H), 1.44 (s, 3 H), 0.82 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (20 MHz, C_6D_6) 175.86, 145.64, 135.75, 82.59, 78.04, 49.76, 43.57, 41.20, 40.35, 39.08, 34.22, 28.82, 27.30, 26.15, 25.12, 20.63, 15.89 ppm; MS, calcd (M^+) m/z 324.1218, obsd 324.1213.

Anal. Calcd for $C_{17}H_{24}O_2S_2$: C, 62.92; H, 7.45. Found: C, 62.69; H, 7.44.

The levororatory enantiomer (1.819 g, 7.32 mmol), $[\alpha]^{25}_D$ −37.5°, yielded the enantiomer of **24** (558 mg, 24%), $[\alpha]^{25}_D$ −14.5° (c 4.77, $CDCl_3$). Analogously, (+)-keto lactone (951 mg, 3.83 mmol), $[\alpha]_D$ +38.3°, furnished (+)-**24** (271 mg, 19%), $[\alpha]^{25}_D$ +10.3° (c 5.04, $CHCl_3$).

(−)-(3*E*,5*R*)-3-Ethylidenedihydro-5-[(6′*R*,7′*R*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-2(3*H*)-furanone (21), the Enantiomer, and Two Dia-

stereomers. Lithium diisopropylamide was prepared in ether (1 mL) from diisopropylamine (0.13 mL, 0.924 mmol) and *n*-butyllithium (0.60 mL, 0.924 mmol, 1.55 M in hexane). The solution was cooled to −60 °C, at which point the levorotatory enantiomer of **24** (250 mg, 0.770 mol), $[\alpha]^{25}D$ −14.5°, dissolved in ether (3 mL) and tetrahydrofuran (2 mL) was added. Enolate formation was permitted to occur during 1.75 h with the temperature of the reaction mixture maintained between −40 and −60 °C. The temperature of the solution was then lowered to −78 °C, and freshly distilled acetaldehyde (0.045 mL, 0.808 mmol) was introduced via syringe. The resulting murky solution was stirred for 4.5 h at −78 °C. The reaction mixture was quenched with saturated ammonium chloride solution (15 mL) and extracted with ether (3 × 20 mL) before being dried and freed of solvent. The condensation product (280 mg, 99%) was obtained as a viscous oil and used without further purification; IR ($CDCl_3$, cm^{-1}) 3600, 3490, 2980, 2940, 2890, 1750, 1628, 1455, 1425, 1365, 1190, 1108, 1065, 1010, 890, 815.

A solution of the condensation product in methylene chloride (4 mL) and triethylamine (0.53 mL, 3.80 mmol) was cooled to 0 °C, and methanesulfonyl chloride (0.24 mL, 3.04 mmol) dissolved in methylene chloride (3 mL) was added dropwise over 40 min. The magnetically stirred reaction mixture was allowed to warm to room temperature with continued stirring for 2 h. The turbid brown solution was partitioned between saturated sodium bicarbonate solution (10 mL) and ether (40 mL). The organic phase was extracted with saturated ammonium chloride solution (20 mL) and brine (20 mL) before drying. Removal of the solvent in vacuo afforded a dark brown oil, which was used immediately.

The crude mesylate was dissolved in benzene (50 mL) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 mL, 3.32 mmol), and the reaction mixture was heated at reflux overnight, cooled, diluted with ether (60 mL), and sequentially washed with saturated sodium bicarbonate solution (2 × 25 mL), saturated ammonium chloride solution (2 × 25 mL), and brine (25 mL) before drying and concentration in vacuo. The residue was purified by MPLC (silica gel; elution with 25% ethyl acetate in petroleum ether) to furnish the ethylidene lactone (130 mg, 49%) as a light yellow oil: $[\alpha]^{22}D$ −41.6° (*c* 0.540, $CHCl_3$); IR (CCl_4, cm^{-1}) 2960, 2920, 2880, 1760, 1685, 1630, 1435, 1332, 1275, 1215, 1130, 993; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73–6.66 (m, 1 H), 4.88 (dd, *J* = 8.8, 5.7 Hz, 1 H), 3.38–3.10 (series of m, 4 H), 2.77 (qt, *J* = 8.7, 2.3 Hz, 1 H), 2.39–2.01 (series of m, 6 H), 1.87–1.58 (series of m, 4 H), 1.85 (dt, *J* = 7.1, 1.9 Hz, 3 H), 1.47 (s, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.00, 146.82, 134.48, 133.91, 128.30, 80.47, 77.55, 48.87, 43.73, 41.45, 40.49, 38.73, 34.05, 28.51, 27.50, 26.20, 20.54, 16.09, 15.82 ppm; MS, calcd (M^+) *m/z* 350.1374, obsd 350.1377.

The enantiomer was prepared in like manner from (+)-**24** (271 mg, 0.835 mmol), $[\alpha]^{25}D$ +10.3°. The intermediate condensation product was obtained in 98% yield and the ethylidene lactone was produced with 38% efficiency, $[\alpha]^{22}D$ +36.3° (*c* 2.39, $CHCl_3$).

(−)-Ethylidene lactone **21** (52 mg, 21%) was comparably generated from (+)-**20** (275 mg, 0.849 mmol), $[\alpha]D$ +5.7°, through the condensation product prepared with 84% efficiency: IR ($CDCl_3$, cm^{-1}) 3610, 3460, 2970, 2940, 1745, 1630, 1445, 1435, 1375, 1265, 1195, 1100, 1020, 890, 810; MS, calcd (M^+) *m/z* 368.1480, obsd 368.1487.

The dextrorotatory enantiomer of **21**, $[\alpha]^{23}D$ +27.5° (*c* 0.415, $CHCl_3$) and mp 101–104 °C, was obtained in 28% yield as an off-white solid from the (−) form of lactone **20** (364 mg, 1.12 mmol), $[\alpha]^{25}D$ −12.0°: IR ($CHCl_3$, cm^{-1}) 2935, 1745, 1685, 1460, 1380, 1332, 1277, 1140, 1067, 980; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76–6.67 (m, 1 H), 4.90 (t, *J* = 7.8 Hz, 1 H), 3.38–3.05 (series of m, 4 H), 2.80–2.70 (m, 1 H), 2.45–2.01 (series of m, 6 H), 1.83 (dt, *J* = 7.2, 1.9 Hz, 3 H), 1.80–1.57 (series of m, 4 H), 1.48 (s, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.99, 145.34, 135.94, 133.90, 128.79, 80.73, 77.59, 49.27, 43.87, 40.89, 40.29, 38.70, 33.96, 29.16, 27.09, 26.02, 19.83, 16.55, 15.62 ppm; MS, calcd (M^+) *m/z* 350.1374, obsd 350.1419.

Independent Synthesis of (−)-3 and Its Enantiomer. Lithium isopropylcyclohexylamide was prepared in tetrahydrofuran (1 mL) from *n*-butyllithium (0.143 mL, 0.222 mmol, 1.55 M in hexane) and isopropylcyclohexylamine (0.036 mL, 0.222 mmol). This solution was cooled to −78 °C, and (−)-**21** (52 mg, 0.148 mmol) dissolved in tetrahydrofuran (2 mL) was introduced via syringe. The enolate was permitted to form during 3 h. HMPA (0.026 mL, 0.148 mmol) and methyl iodide (0.014 mL, 0.222 mmol) were added sequentially, and stirring was continued at −78 °C for 5 h. The reaction mixture was quenched with water (10 mL) and extracted with saturated ammonium chloride solution (10 mL). The combined aqueous phases were back-extracted with ether (2 × 10 mL), and the combined organic phases were dried and freed of solvent. The crude product was purified by MPLC (silica gel; elution with 7.5% ethyl acetate in petroleum ether), yielding (−)-**3** (20 mg, 36%), $[\alpha]^{25}D$ −10.0° (*c* 1.69, $CHCl_3$) as a light yellow oil having spectral properties identical with those of the product of degradation isolated earlier.[37b]

(3*RS*,5*SR*)-Dihydro-3-methyl-5-[(6′*SR*,7′*SR*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-2(3*H*)-furanone (22). Lactone **22** was prepared from **20** (448 mg, 1.38 mmol) according to the procedure described below for **25**. Recovered starting material (70 mg) was separated from the desired product (255 mg, 55% or 65% based on recovered starting material) by MPLC (silica gel; elution with 10% ethyl acetate in petroleum ether). Methylated lactone **22** was obtained as an off-white solid: mp 57.5–60.0 °C; IR (C_6D_6, cm^{-1}), 2965, 1780, 1465, 1430, 1380, 1253, 1195, 862, 695; ^1H NMR (200 MHz, C_6D_6) δ 4.65 (t, *J* = 7.5 Hz, 1 H), 2.98–2.68 (m, 4 H), 2.49–2.32 (m, 4 H), 2.09–1.34 (series of m, 8 H), 1.59 (s, 3 H), 1.03 (d, *J* = 7.4 Hz, 3 H), 0.99 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (20 MHz, C_6D_6) 178.99, 144.81, 137.27, 80.68, 78.18, 49.69, 44.26, 41.52, 40.43, 38.83, 35.26 34.11, 33.92, 27.27, 26.25, 20.12, 16.67 (2 C) ppm; MS, calcd (M^+) *m/z* 338.1374, obsd 338.1438.

(±)-(3*RS*,5*RS*)-Dihydro-3-methyl-5-[(6′*RS*,7′*RS*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-3-vinyl-2(3*H*)-furanone (23). Lithium diisopropylamide was prepared from diisopropylamine (0.08 Ml, 0.56 mmol) and *n*-butyllithium (0.35 mL, 0.56 mmol, 1.60 M in hexane) in ether (2 mL). The solution was cooled to −78 °C, and **22** (127 mg, 0.377 mmol) dissolved in ether (1 mL) was added via syringe. After the mixture was stirred 1 h, (phenylseleno)acetaldehyde (90 mg, 0.452 mmol) was added. After 5 h, the reaction mixture was quenched with water, subsequently extracted with ether, dried, and concentrated under reduced pressure. The crude aldol intermediate was immediately dissolved in methylene chloride (3 mL) and transferred to a 25-mL flask equipped with an addition funnel. Triethylamine (0.27 mL, 1.92 mmol) was added dropwise, followed by methanesulfonyl chloride (0.12 mL, 1.55 mmol) dissolved in methylene chloride (2 mL) over 1 h. After 30 min, the reaction mixture was diluted with methylene chloride and washed with saturated sodium bicarbonate solution and water. The aqueous washes were combined and extracted with methylene chloride. The combined organic washes were dried and concentrated in vacuo. Purification was achieved by MPLC (silica gel; elution with 5% ethyl acetate in petroleum ether). Recovered starting material (5 mg) was isolated alongside **23** (30 mg, 22%), a yellow oil: IR (CCl_4, cm^{-1}) 2940, 1780, 1640, 1460, 1380, 1125, 685; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 17.4, 10.5 Hz, 1 H), 5.17 (d, *J* = 16.8 Hz, 1 H), 5.16 (d, *J* = 10.8 Hz, 1 H), 4.67 (dd, *J* = 11.3, 5.4 Hz, 1 H), 3.39–3.14 (series of m, 4 H), 2.42–2.06 (series of m, 8 H), 1.70–1.62 (m, 3 H), 1.51 (s, 3 H), 1.34 (s, 3 H), 1.03 (d, *J* = 6.7 Hz, 3 H); MS, calcd (M^+) *m/z* 364.1531, obsd 364.1506.

(3*RS*,5*SR*)-Dihydro-3-methyl-5-[(6′*RS*,7′*RS*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-2(3*H*)-furanone (25). Lithium diisopropylamide was prepared from diisopropylamine (0.23 mL, 1.62 mmol) and *n*-butyllithium (1.01 mL, 1.62 mmol, 1.60 M in hexane) in tetrahydrofuran (4 mL). This solution was cooled to −78 °C, and **24** (439 mg, 1.35 mmol) dissolved in tetrahydrofuran (5 mL) was added dropwise. After 1 h, HMPA (0.23 mL, 1.32 mmol) and methyl iodide (0.10 mL, 1.62 mmol) were added. Stirring was continued for 8 h at −78 °C, followed by warming to 0 °C over 2 h. The reaction mixture was quenched with water, extracted with ether, and dried. After concentration in vacuo, MPLC (silica gel; elution with 10% ethyl acetate in petroleum ether) was used to separate the recovered starting material (97 mg) from the desired **25** (249 mg, 55% or 70% based on recovered starting material), a yellow oil: IR (C_6D_6, cm^{-1}) 2980, 1790, 1435, 1385, 1260, 1205, 1015, 865, 745, 705; ^1H NMR (200 MHz, C_6D_6) δ 4.79 (dd, *J* = 8.1, 5.9 Hz, 1 H), 3.39–3.08 (series of m, 4 H), 2.95–1.51

(series of m, 12 H), 1.46 (s, 3 H), 1.25 (d, J = 7.3 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (20 MHz, C_6D_6) 178.83, 146.36, 135.42, 80.37, 78.07, 49.47, 43.74, 41.77, 40.57, 38.76, 34.61, 34.28, 32.91, 27.61, 26.13, 20.12, 16.40, 15.91 ppm; MS, calcd (M^+) m/z 338.1374, obsd 338.1331.

(3*RS*,5*RS*)-Dihydro-3-methyl-5-[(6′*SR*,7′*SR*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-3-vinyl-2(3*H*)-furanone (26). Lactone **26** was prepared in a manner identical with **23**. After purification, **26** (28 mg, 23%) was obtained from **25** (111 mg, 0.328 mmol) as a yellow oil: IR (CCl_4, cm^{-1}) 2980, 2940, 1780, 1635, 1440, 1380, 1130, 1020, 925, 690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dd, J = 17.4, 10.5 Hz, 1 H), 5.18 (d, J = 17.4 Hz, 1 H), 5.17 (d, J = 10.2 Hz, 1 H), 4.74 (dd, J = 11.6, 5.4 Hz, 1 H), 3.39–3.16 (m, 4 H), 2.66–2.03 (series of m, 8 H), 1.73–1.59 (m, 3 H), 1.45 (s, 3 H), 1.34 (s, 3 H), 0.98 (d, J = 6.6 Hz, 3 H); MS, calcd (M^+) m/z 364.1530, obsd 364.1529.

(+)-(3*R*,5*S*)-Dihydro-3-methyl-5-[(6′*R*,7′*R*)-4′,5′,6′,7′-tetrahydro-6′,7′-dimethylspiro[1,3-dithiolane-2,1′-indan]-7′-yl]-3-vinyl-2(3*H*)-furanone (27) and Its Enantiomer. Lactone **27** (27.8 mg, 51%), $[\alpha]^{25}_D$ +6.3° (c 1.06, $CHCl_3$), was produced from (+)-**24** (53.0 mg, 0.151 mmol), $[\alpha]^{22}_D$ +36.3°, in a manner analogous to that previously described for its diastereomers. Likewise, (−)-**24** (110 mg, 0.314 mmol), $[\alpha]^{22}_D$ −41.6°, yielded (−)-**27** (23 mg, 20%), $[\alpha]^{23}_D$ −14.0° (c 1.07, $CHCl_3$), as a yellow oil: IR ($CHCl_3$, cm^{-1}) 2965, 2930, 2880, 2840, 1765, 1644, 1456, 1375, 1340, 1198, 1155, 1100, 990, 850; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (dd, J = 17.5, 10.6 Hz, 1 H), 5.19 (d, J = 17.3 Hz, 1 H), 5.19 (d, J = 10.8 Hz, 1 H), 4.91 (dd, J = 11.5, 5.6 Hz, 1 H), 3.40–3.16 (series of m, 4 H), 2.69 (t, J = 12.1 Hz, 1 H), 2.42–2.04 (series of m, 6 H), 1.98 (dd, J = 12.7, 5.6 Hz, 1 H), 1.75–1.48 (series of m, 3 H), 1.46 (s, 3 H), 1.35 (s, 3 H), 1.00 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 179.45, 145.54, 140.15, 135.09, 114.52, 80.15, 77.73, 49.42, 46.48, 42.75, 40.81, 40.06, 38.24, 34.00, 27.12, 26.31, 26.26, 22.32, 20.94, 16.09 ppm; MS, calcd (M^+) m/z 364.1531, obsd 364.1540.

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(+)-Pleuromutilin Synthetic Studies. Direct Degradation to and Independent Preparation of an Advanced Diketone Intermediate. Demonstration that Reconstruction of the Eight-Membered Ring Suffers from Serious Kinetic Retardation

Leo A. Paquette,* Philip C. Bulman-Page,[1] Paul D. Pansegrau, and Paul E. Wiedeman[2]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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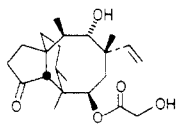
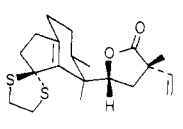
Levorotatory lactone **2** has been converted into (−)-bicyclic ketone **3**, an intermediate containing all 20 carbon atoms of the pleuromutilin target. Pleuromutilin and tiamulin have in turn been degraded to this important relay compound in only four steps. Various methods for achieving the chemoselective functionalization of **3** are described as a prelude to intramolecular closure of the eight-membered ring. The significant kinetic retardation associated with this process is set in focus.

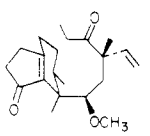
In the preceding paper,[3] an account is given of the degradation of pleuromutilin (**1**) and tiamulin to the levorotatory tricyclic lactone **2**, and the successful implementation of a strategy for de novo synthesis of the latter. These studies established the feasibility of incorporating all of the essential structural features associated with the western sector of these antibiotics, while also providing for a convenient source of **2**. In order to arrive at this first relay point, it was necessary to excise an ethyl group from **1**, in expectation that its later reintroduction could be readily accomplished. Herein, we address the challenge



1



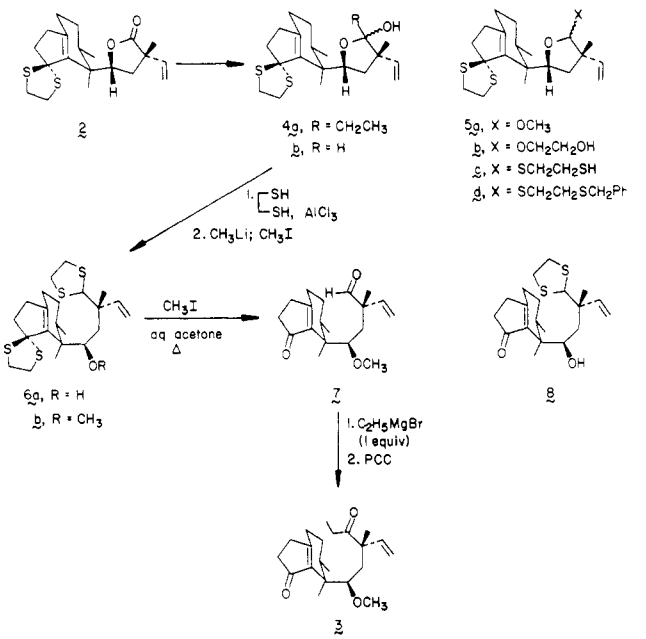
2



3

of transforming (−)-**2** to (−)-**3**. In addition, we report on the readiness with which this *second* relay intermediate can be produced from (+)-**1** and tiamulin.[4] Finally, preliminary experiments aimed at the fundamental problem of reclosing the eight-membered ring are described.

Scheme I



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(3) Paquette, L. A.; Wiedeman, P. E.; Bulman-Page, P. C. *J. Org. Chem.*, preceding paper in this issue.

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