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A RELAY APPROACH TO (+)-PLEUROMUTILIN. I. DE NOVO SYNTHESIS OF A LEVOROTATORY TRICYCLIC LACTONE SUBUNIT

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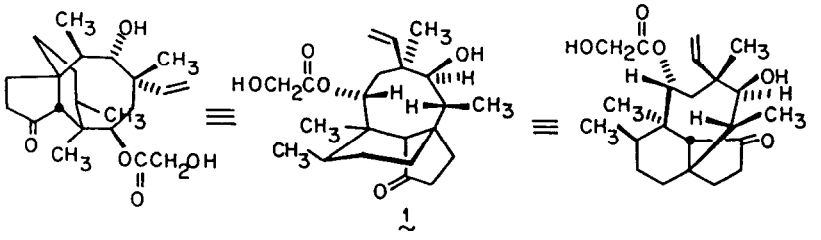
Summary: Construction of the optically active lactone (-)-13, required for a proposed total synthesis of (+)-pleuromutilin, has been successfully achieved.

The molecular array present in (+)-pleuromutilin (1), a structurally unusual diterpene antibiotic produced by several basidiomycetes[2] via an unprecedented biosynthetic pathway,[3] is comprised of a rather rigid tricyclic carbon network. Prominent in its structure are eight stereogenic centers, seven of which are positioned consecutively on the eight-membered ring. The substance, which also carries three quaternary carbon atoms, is prone to unusual chemical reactivity[4] and is thus a challenging synthetic target.[5] Accordingly, we have set out to prepare 1 in its proper absolute configuration.

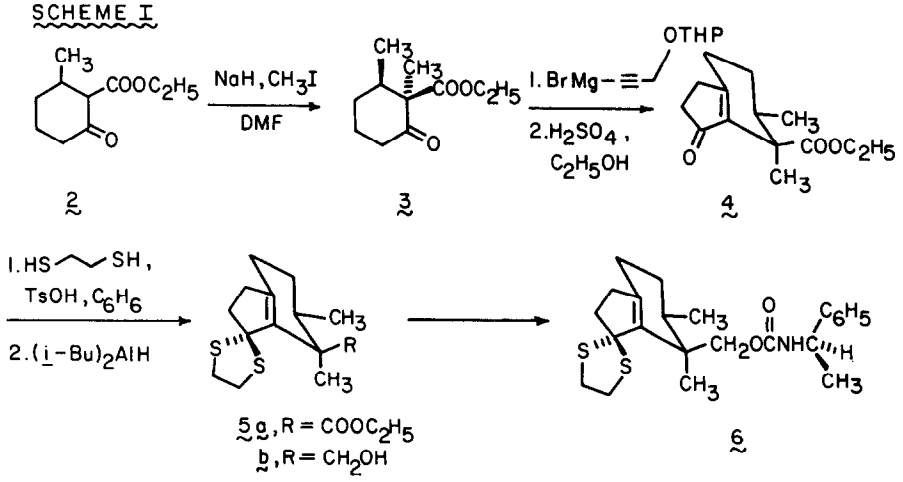


The overall strategy involves merger of a practical synthesis of an advanced intermediate in resolved form with a short degradation of the natural product. Such relay methodology is more expeditious than a classical serial approach and allows more extensive investigation of options at various points in the synthetic pathway. Retrosynthetic logic suggested that our purposes might be served by gaining access to the obligatory levorotatory enantiomer of 13, wherein four centers of asymmetry have been installed with the appropriate

absolute stereochemistry.[6]

Conveniently, the relatively inexpensive cyclohexanone carboxylate **2**[7] proved to be three short steps away from bicyclic keto ester **4** (Scheme I). The methylation of **2** is stereoselective, leading predominantly to **3** (81%).[8] Separation of **3** on large scale from its epimer and dimethylated product was achieved by spinning band distillation. The procedure most effective for cyclopentenone annulation (49% overall yield) proved to be that introduced by Raphael.[9] With secure supplies of **4** in hand, we proceeded to protect the ketone carbonyl group. No ketalization was observed upon heating **4** with various 1,2- and 1,3-glycols in the presence of acid, indicating that substantial steric shielding was operative at that site. Nonetheless, experiments involving the more nucleophilic 1,2-ethanedithiol efficiently afforded **5a** (95%), reduction of which with Dibal-H provided the important alcohol **5b** (91%).

SCHEME I



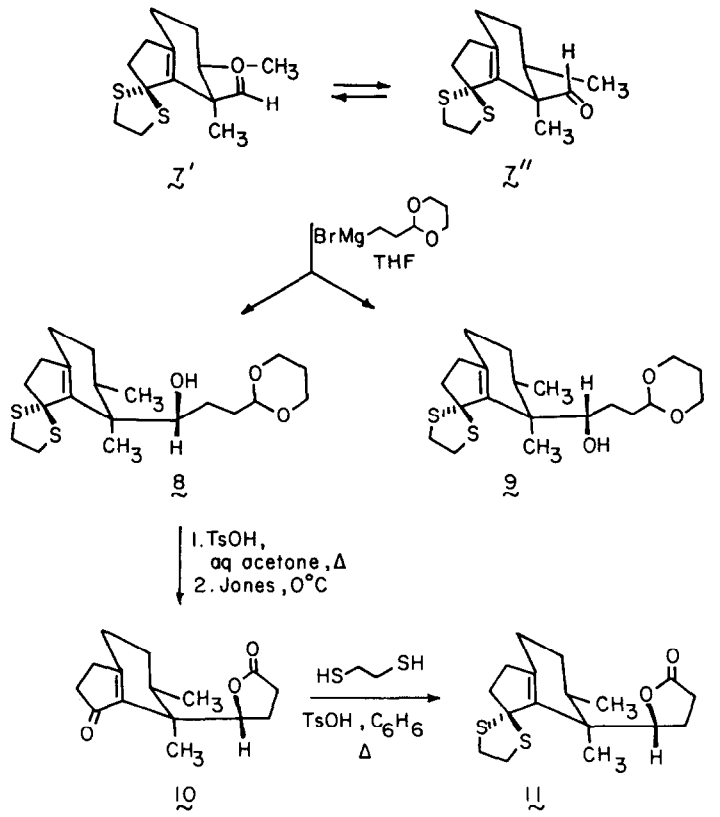
5a, R = $COOC_2H_5$
5b, R = CH_2OH

6

Both enantiomers of **5b** were obtained by reaction with (R)-(+)-α-methylbenzyl isocyanate (cat. DMAP, toluene, reflux), separation of the diastereomeric carbamates (**6**) by HPLC on silica gel, and individual treatment with trichlorosilane and triethylamine in hot toluene[10]. ^1H NMR studies with tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III) established the $[\alpha]_D^{20}$ of optically pure **5b** in $CHCl_3$ to be 38.9°.

Following Collins oxidation of the dextrorotatory alcohol,[11] aldehyde **7** was condensed with the functionalized Grignard reagent depicted in Scheme II. Although molecular models of **7**, $[\alpha]_D^{20}$ +111.3° ($CHCl_3$), showed little preference for adoption of the primed or doubly

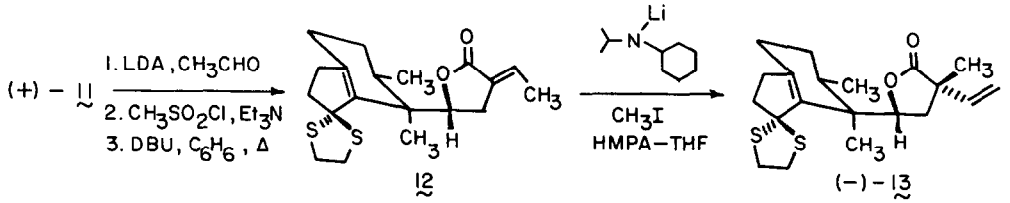
SCHEME II



primed conformation, both structures were clearly seen to be blockaded to attack from that direction cofacial with the dithioketal. In line with this analysis, a 1:1 mixture of **8**, $[\alpha]_D^{20}$ -0.5° ($CHCl_3$), and **9**, $[\alpha]_D^{20}$ +8.5° ($CHCl_3$), was obtained. Chromatographic separation of these isomers proved to be remarkably facile (91% combined yield).

The critical lactone ring was now elaborated by acid hydrolysis of **8** and subsequent Jones oxidation. Optically pure **10** has $[\alpha]_D^{20}$ -14.6° ($CHCl_3$). Reexposure to 1,2-ethanedithiol resulted in suitable differentiation of the enolizable sites.

SCHEME III



The size and location of the bicyclic moiety on the butyrolactone substructure in **11**, $[\alpha]_D^{20}$ +5.7 ° ($CHCl_3$), dictated the order of introduction of the final two substituents. Aldol condensation of the lithium enolate with acetaldehyde and subsequent ß-elimination via the mesylate[12] afforded **12** (Scheme III). Deconjugative methylation of **12** with LICA in tetrahydrofuran containing a small amount of HMPA delivered **13** as a single levorotatory stereoisomer (56%), identical in all respects with the degradation product described in the adjoining report.[6]

In summary, a scheme for properly integrating the four stereocenters in (-)-**13** has been successfully implemented. This intermediate, which corresponds to a significant subsection of the target pleuromutilin molecule, will now be shown to be readily obtainable by degradation of the natural product.[6]

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References and Notes

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8. All new compounds described herein gave correct elemental analysis and/or accurate mass spectral data. All ^1H NMR, ^{13}C NMR, and IR spectra are also in accord with the assigned structures.
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