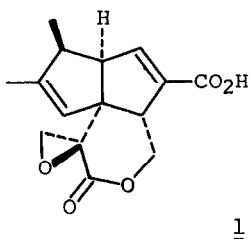


SYNTHESIS OF SESQUITERPENE ANTITUMOR LACTONES. 7.<sup>1</sup>  
STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF PENTALENOLACTONE.  
INTRAMOLECULAR ENE REACTION.

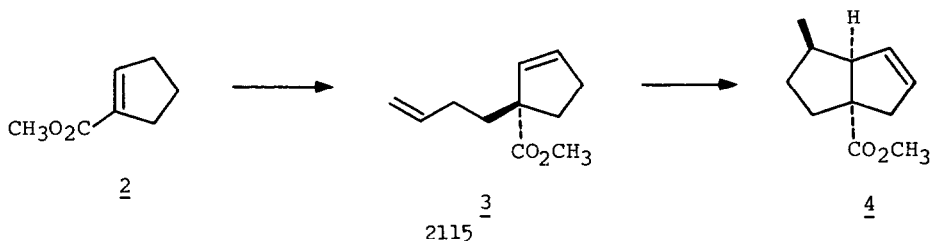
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Functionalized cyclopentene 11 is cyclized via thermal ene reaction to 12. All steps in the synthesis of 12 are highly stereoselective.

Pentalenolactone (1) is an acidic lipophilic antibiotic which has been isolated from various *Streptomyces* strains.<sup>2</sup> Because of its unique structure, compound 1 presents an interesting synthetic challenge. One total synthesis of pentalenolactone has been published.<sup>3</sup> At this time we wish to report our own studies which show promise as a more direct approach to this antibiotic.



Alkylation of  $\alpha,\beta$ -unsaturated ester 2 with 4-bromo-1-butene (LDA, THF, HMPA,  $-70^\circ\text{C}$ ) affords unsaturated ester 3 in 75% yield. Ester 3 is vaporized through a heated tube (ca.  $500^\circ\text{C}$ ) to provide unsaturated ester 4 in 93% yield.

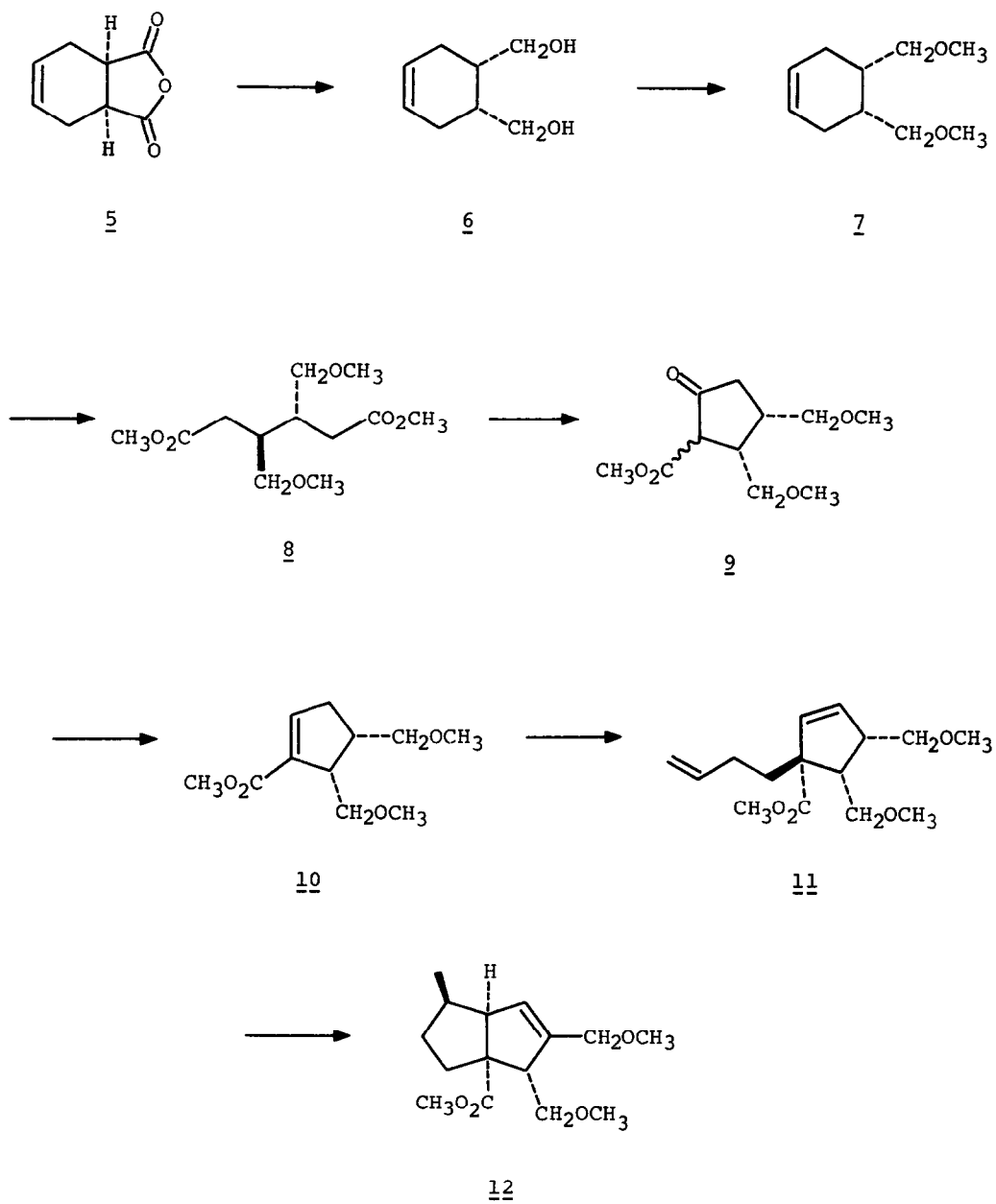


The  $^{13}\text{C}$ -NMR spectrum of compound 4 shows that the intramolecular ene reaction is highly stereoselective; no other diastereomer may be detected. Furthermore, the chemical shift of the methyl group ( $\delta = 15.6$  ppm) demonstrates conclusively that it is endo.<sup>4</sup>

With this transformation in hand, the synthetic problem is reduced to the construction of a properly functionalized cyclopentene. The readily available<sup>5</sup> cis-anhydride 5 is reduced ( $\text{LiAlH}_4$ , THF) to the cis-diol<sup>6</sup> (6) in 89% yield. Dimethyl ether 7 is formed ( $\text{NaH}$ , MeI, THF) in 84% yield and is oxidatively cleaved ( $\text{O}_3$ , MeOH;  $\text{HCO}_2\text{H}$ ,  $\text{H}_2\text{O}_2$ ;  $\text{CH}_2\text{N}_2$ , ether) to diester 8 in 91% yield. Dieckmann cyclization ( $\text{NaH}$ , THF,  $\Delta$ ) affords  $\beta$ -keto ester 9 in 78% yield. Reduction by sodium borohydride in methanol followed by dehydration ( $\text{TsCl}$ , pyridine;  $\text{NaOMe}$ , MeOH) gives  $\alpha,\beta$ -unsaturated ester 10 in 58% yield. Ester 10 is alkylated with 4-bromo-1-butene ( $\text{LDA}$ , THF, HMPA,  $-70^\circ\text{C}$ ) to provide 11 in 72% yield. The alkylation of ester 10 appears to be highly stereoselective; compound 11 is obtained in greater than 95% purity, as judged by glpc and  $^{13}\text{C}$ -NMR spectroscopy. Upon heating in a sealed tube ( $345^\circ\text{C}$ , 40 min), ester 11 cyclizes to compound 12 in 71% yield.<sup>7</sup>

As can be seen, compound 12 embodies several salient features of the pentalenolactone structure. The key step in this model study (3  $\rightarrow$  4) is inspired by previous applications of intramolecular ene reactions in the construction of bicyclic heterocycles.<sup>8</sup> Further work toward application of this method to the synthesis of pentalenolactone is underway.

*Acknowledgment.* Support for this research was provided by a grant from the National Institutes of Health (no. CA-12617).



*References and Notes*

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(Received in USA 27 March 1979)