

## Synthesis of a Rigid Diacylglycerol Analogue Having a Bis- $\gamma$ -butyrolactone Skeleton Separated by a Cyclopentane Ring

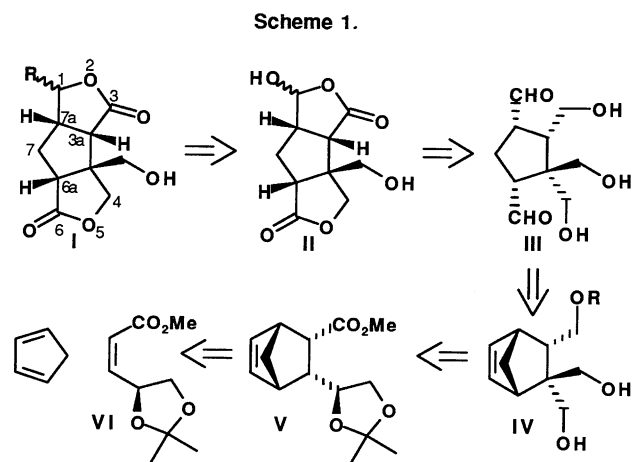
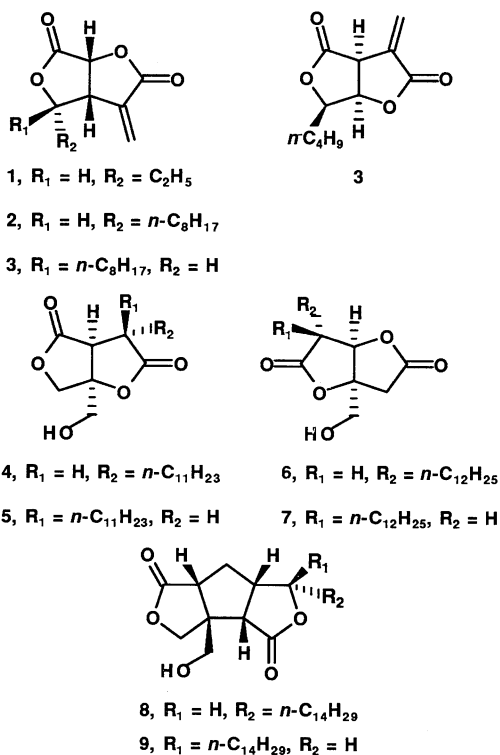
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A very efficient method for the construction of a new bis- $\gamma$ -lactone system constructed on a cyclopenta[1,2-*c*:3,4-*c'*]perhydrodifuran scaffold was developed from cyclopentadiene and methyl (S)-(Z)-4,5-*O*-isopropylidene-pent-2-enoate.

The bis- $\gamma$ -lactone skeleton common to some natural products, such as ethisiolide (1), isoavenaciolide (2), avenaciolide (3) and canadensolide (3), have attracted the attention of chemists and pharmacologists alike due to their biological activity.<sup>1,2</sup> In our own laboratory, we have recently synthesized several related bis- $\gamma$ -lactones (i.e., 4-7) as molecular scaffolds for the construction of rigid diacylglycerol (DAG) analogues.<sup>3,4</sup> The latter compounds can indeed function as DAG surrogates and bind to the DAG target, protein kinase C (PK-C), with micromolar affinities.<sup>3,4</sup> Since in all of these structures the two lactone rings are contiguous, we decided to investigate the synthesis of bis- $\gamma$ -lactones separated by a spacer ring.

The first example of such an effort is represented by the attempted synthesis of the cyclopenta[1,2-*c*:3,4-*c'*]perhydrofuran analogues (8 and 9) which were designed as PK-C agonists by additionally attaching to the molecule a hydroxymethyl substituent and a lipophilic alkyl chain.



The retrosynthetic analysis of templates I/II via the polyfunctional cyclopentane III is outlined in Scheme 1. This intermediate was envisioned to originate from the chiral norbornene IV which, in turn, was expected to come from the Diels-Alder adduct V derived from cyclopentadiene and the chiral methyl (Z)-pentenoate ester VI. The cycloaddition was expected to proceed with the anticipated *syn-endo* diastereoselectivity where the cyclopentadiene approaches the dienophile VI from the same side as the allylic oxygen function.<sup>5</sup> Indeed, as shown in Scheme 2, the optically pure *syn-endo* adduct 10 was readily prepared.<sup>5</sup> Because of its susceptibility to epimerization,<sup>6</sup> the ester group in 10 was reduced and protected as a benzyl ether (compound 12). The isopropylidene group of 12 was then removed and the resulting diol 13 was cleaved with sodium metaperiodate to give aldehyde 14. Aldol condensation of 14 with excess formaldehyde, followed by an *in situ* Cannizzaro reaction gave the bis-hydroxymethyl derivative 15 in excellent yield.<sup>7</sup> Osmium tetroxide cleavage of the double bond in 15 produced a transient dialdehyde which cyclized immediately to an equilibrium mixture of hemiacetals 16 and 17. The first intramolecular cyclization automatically fixed the stereochemistry of the hydroxymethyl group at the bridgehead because the proximal aldehyde reacted only with the hydroxymethyl group on the same side of the cyclopentane ring. Further reaction of one epimer of hemiacetal 16 with the second aldehyde group gave the tricyclic hemiacetal 17. Treatment of the 16/17 mixture under basic conditions with *tert*-butylchlorodiphenylsilane accomplished both protection of the primary alcohol and epimerization of the second aldehyde function to give 18 as a single product.<sup>8</sup> Since hemiacetal formation from the convex face of the molecule is impossible, the stereochemistry of the aldehyde function had to be "up" as indicated. Oxidation of 18 to lactone 19 was uneventful and removal of the benzyl ether protection gave hydroxy-aldehyde 20. Formation of this product confirmed the stereochemistry of the free aldehyde-bearing carbon which was subsequently re-epimerized in the

