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Stereostructural Studies on the 4-Hydroxylated Annonaceous Acetogenins: Synthesis of Model Butenolides of Known Relative and Absolute Configuration Involving an Intriguing Translactonization Reaction

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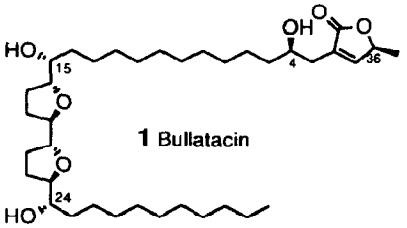
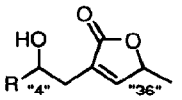
Abstract: *Each diastereomer of model butenolides 3 was synthesized from appropriate antipodes of two propylene oxide molecules. Concomitant translactonization reactions have important stereochemical ramifications.*

The Annonaceous acetogenins are a remarkable class of naturally occurring antitumor agents, and those possessing a hydroxyl substituent in the C(4) position are among the most potent in this class[2] (cf. bullatacin, **1**[3]). No general method for determining either the absolute or relative configuration of C(4)/C(36) in C(4)-hydroxylated Annonaceous acetogenins existed prior to the work described here. Structural studies to address this issue[4,5] required us to prepare model butenolides **2**, bearing C(4) and C(36) stereocenters (bullatacin numbering) analogous to the natural products. Initially, we identified compound **2**, bearing a side chain derived from 1,2-epoxydodecane, as an excellent model for the straight carbon chain of the 4-hydroxy acetogenins. Accordingly, we prepared (±)-2-phenylthio-4-methylbutyrolactone (**4**) from 2-(phenylthio)acetic acid and (±)-propylene oxide.[6] Alkylation of the lithium



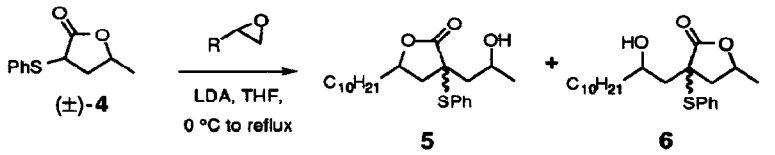
1 Bullatacin



2 R=$C_{10}H_{21}$
3 R=CH_3

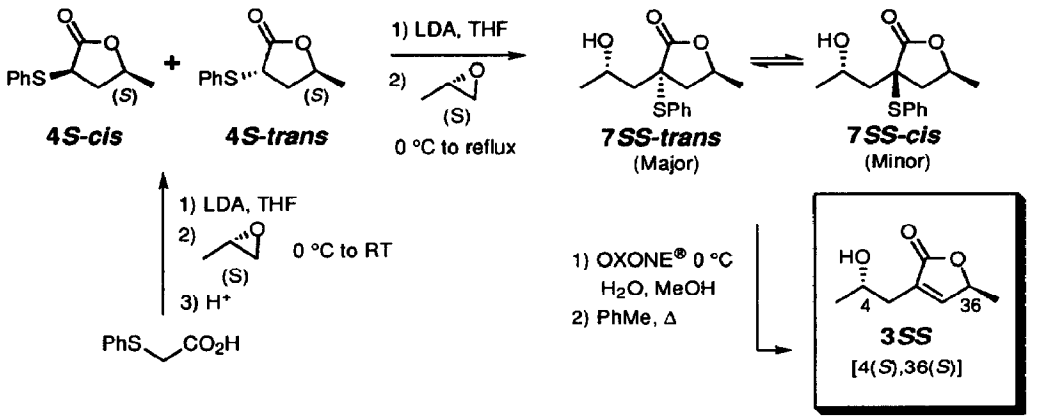
enolate derived from this lactone with 1,2-epoxydodecane, however, produced a mixture of regioisomers **5** and **6** (Scheme 1), indicating that an internal translactonization had occurred.[7] Efforts to solve this problem by changing the order of steps or blocking one hydroxyl group from participating in translactonization proved cumbersome, although such a strategy has successfully been used in syntheses of (-)-*ent*-bullatacin[8] and rolliniastatin I.[9,10]

Scheme 1



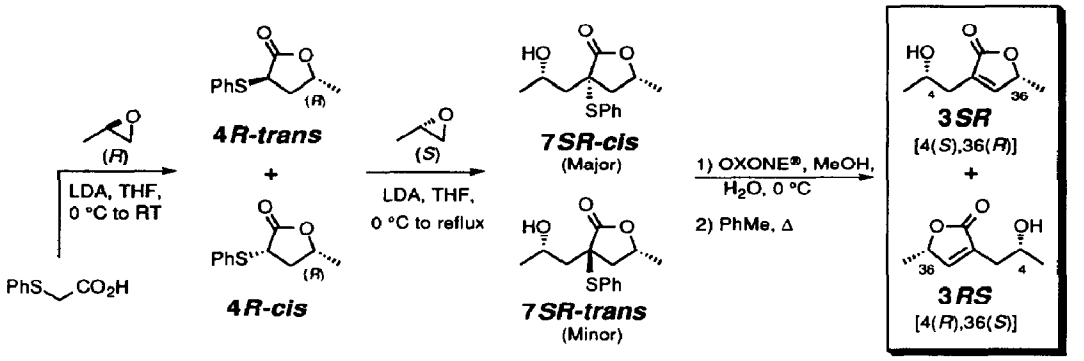
To circumvent this problem, we targeted, instead, the more symmetrical model lactone **3**, which could be prepared by sequential alkylation of 2-(phenylthio)acetic acid with two equivalents of propylene oxide. Judicious use of the individual enantiomers of propylene oxide reduces the complicating translactonization to an issue of stereochemistry rather than regiochemistry. Thus, the model compound ***3SS***, a "like" diastereomer, was prepared in three steps from (phenylthio)acetic acid (Scheme 2). Initial alkylation of the dianion of (phenylthio)acetic acid (2.0 equivalents LDA, THF, 0 °C) with (*S*)-propylene oxide followed by lactonization (cat. H_2SO_4, C_6H_6) yielded an approximately 1:1 mixture of the 4-methyl-2-phenylsulfenyl-γ-butyrolactones, ***4S-cis*** and ***4S-trans***, in 83% yield.[6] Alkylation of this mixture (LDA, THF, 0 °C, 1h) with a second (*S*)-propylene oxide unit in refluxing THF yielded a mixture (inseparable on SiO_2) of the nonracemic phenylthiolactones ***7SS-trans*** and ***7SS-cis*** in an approximate 5:1 ratio, respectively, and 64% overall yield. Subsequent oxidation of the mixture with Oxone® gave four diastereomeric sulfoxides, which were eliminated in refluxing toluene to converge at a nonracemic sample of the model butenolide ***3SS*** [67% yield, $[\alpha]_D^{RT}$ = +82.7 (c = 1.11, $CHCl_3$)], unambiguously containing the 4*S*,36*S* (or "like") configuration.

Scheme 2



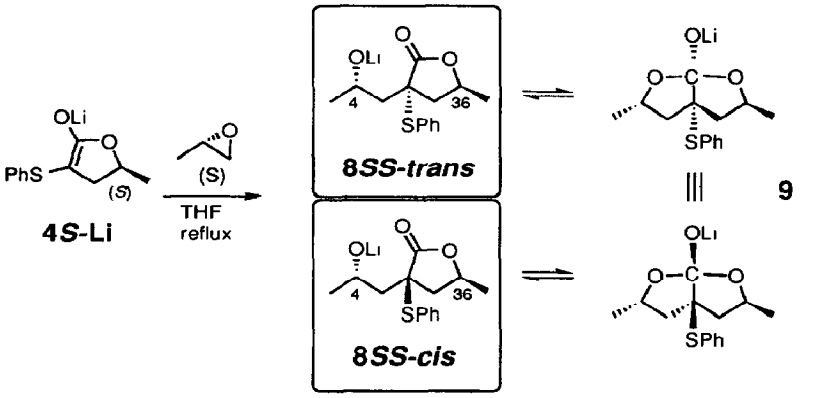
For the "unlike" diastereomer (Scheme 3), lactones ***4R-trans*** and ***4R-cis***, prepared from (*R*)-propylene oxide, were alkylated (LDA, THF, 0 °C, 1h) with (*S*)-propylene oxide to give the SiO_2-separable, *racemic cis-* and *trans*-phenylthiolactones ***7SR-cis*** (38%) and ***7SR-trans*** (6%).[11] A sample containing both diastereomers of **7** was oxidized with Oxone® and eliminated at reflux in toluene to give the *racemic* "unlike" butenolide ***3SR /3RS*** in 63% yield. The origin of the racemization lies in the translactonization events.

Scheme 3



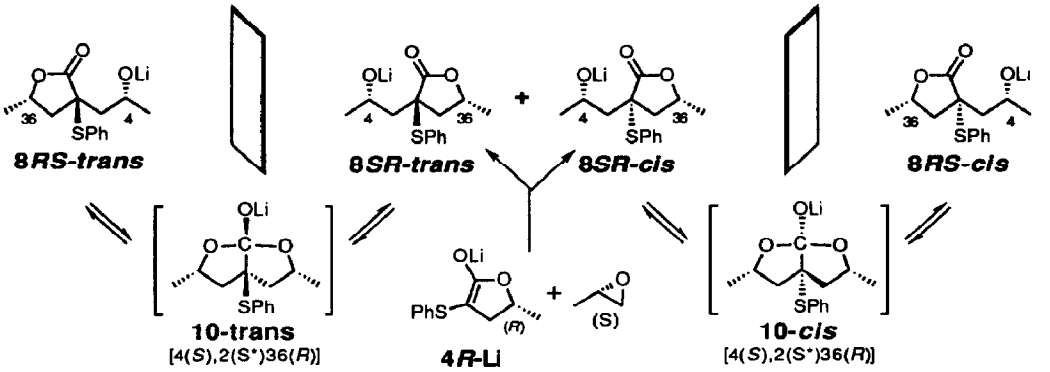
A closer look at the translactonization process in both the "like" and "unlike" series (Schemes 4 and 5, respectively) suggests that the product ratios of **7** are controlled by different factors. Alkylation of the lithium enolate **4*S*-Li** with (*S*)-propylene oxide results in a 5:1 ratio of **7*SS-trans*** to **7*SS-cis*** (Scheme 2). As shown in Scheme 4, translactonization of the initial, kinetically controlled mixture of alkoxides **8*SS*-trans** and **8*SS*-cis** can proceed through the common, cis-fused, tetrahedral intermediate **9**, which would place the two diastereomeric alkoxides in equilibrium with one another. The final 5:1 product ratio therefore presumably reflects a thermodynamically controlled equilibrium ratio rather than the initial kinetic preference for attack at either of the two diastereotopic faces of the enolate **4*S*-Li**.

Scheme 4



As shown in Scheme 5, and by contrast, initial alkylation of the lithium enolate **4*R*-Li** with (*S*)-propylene oxide in the "unlike" series generates a mixture in which the cis isomer, **8*SR-cis***, predominates over the trans isomer, **8*SR-trans***. Translactonization within each of these diastereomers, however, would proceed through the two diastereomeric, cis-fused, C_S-symmetric *meso*-tetrahedral intermediates, **10-*trans*** and **10-*cis***. This isomerization places each diastereomeric alkoxide in equilibrium with its enantiomer **8*RS-cis*** (major) and **8*RS-trans*** (minor). The final ratio of 6:1 in the "unlike" series is therefore presumably a measure of the initial kinetic preference for alkylation trans to the methyl group in **4*R*-Li**. The observed complete racemization[11] implies that translactonization is fast under the reaction conditions (refluxing THF).

Scheme 5



To summarize:

- Translactonization of the "like" **8*SS*** alkoxides (Scheme 4) constitutes a diastereomerization;
- Translactonization of the "unlike" **8*SR*** alkoxides (Scheme 5) constitutes an enantiomerization.
- The strategy of using two propylene oxide units for synthesis of appropriate model compounds proved indispensable for unraveling the accompanying complexities.
- The successful synthesis of these model compounds, their subsequent spectroscopic evaluation,[5] and studies on the mechanism of this internal translactonization have implications for the total synthesis of any of the C(4)-hydroxylated acetogenins.[10]

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References and Notes

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10. For an improved strategy for synthesis of the C(4)-hydroxylated butenolide moiety, see Hoye, T. R.; Humpal, P. E.; Jiménez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.*, in press.
11. Samples of the "unlike" compounds ***7RS-trans/7SR-trans*** and ***7RS-cis/7SR-cis*** had essentially no optical rotation. Their racemic nature was confirmed by conversion (oxidation/elimination) to an essentially 1:1 mixture of the enantiomeric butenolides **3*R*S****, whose optical rotation was zero and whose ratio was confirmed by Mosher ester analysis.[5]

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