Pergamon

Tetrahedron Letters, Vol. 37, No. 48, pp. 8703-8706, 1996

0040-4039/96 $15.00 + 0.00

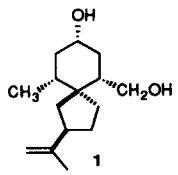
PII: S0040-4039(96)02020-5

Rearrangement of Cyclobutyl Carbinyl Radicals: Total Synthesis of the Spirovetivane Phytoalexin (±)-Lubiminol

Michael T. Crimmins,* Zhuo Wang and Lynne A. McKerlie
Venable and Kenan Laboratories of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599-3290

Abstract: The total synthesis of the phytoalexin (±)-lubiminol **1** has been accomplished. The synthesis relies on a conjugate addition-cyclization reaction to prepare a photosubstrate for a stereoselective intramolecular photoaddition reaction. The photoadduct is transformed into the required spiro [5.4] decane through a radical fragmentation-rearrangement reaction.

Several highly oxygenated spirovetivane phytoalexins[1] have been isolated from potato tubers infected with the fungi *Phytophthora infestans* or *Glomeralla cingulata*.[2] Lubiminol (**1**),[3] lubimin (**2**)[4] and oxylubimin (**3**)[4,5] are the more structurally complex members of this class and are intermediates in the biosynthesis of the potent antifungal agent rishitin (**4**)[6] from acetic acid.[7]



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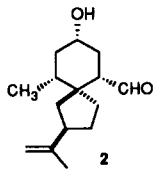

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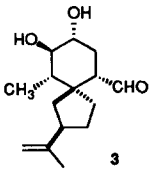

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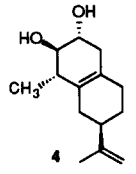
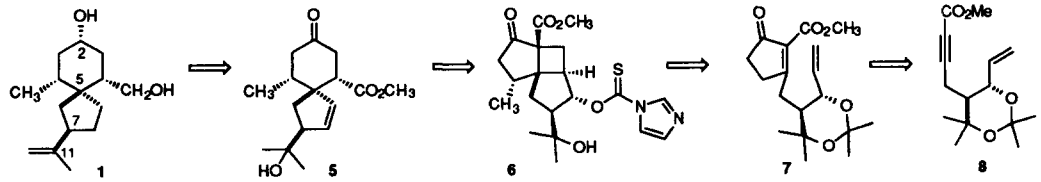


4

Establishing the five (or six) stereogenic centers on the spirocarbocyclic skeleton, particularly the relative stereochemistry of C5 and the remote stereogenic center at C7, is critical to a successful synthesis of any of the members of this class. Previous syntheses[4,5] of these important plant metabolites have utilized a benzenoid aromatic precursor to construct the stereochemically and functionally complex cyclohexane. We report here a unique approach to the synthesis of hydroxylated spirovetivanes and the total synthesis of (±)-lubiminol (**1**).

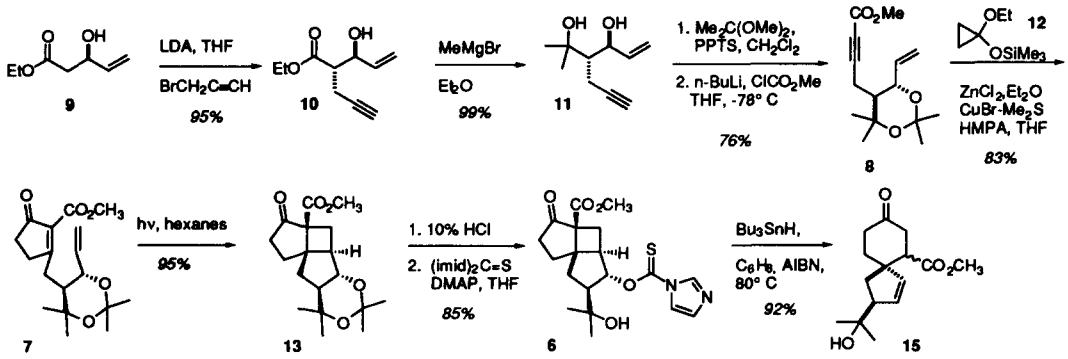
Scheme 1



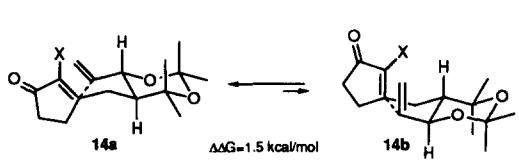
Lubiminol (**1**) would be derived from the functionalized spirocycle **5** which would be the product of the radical fragmentation-rearrangement sequence described previously[8,9] starting with thiocarbamate **6**. A stereoselective photocycloaddition[10] of enone-alkene **7** would provide access to the radical precursor **6**. In turn,

enone **7** would be prepared from acetylenic ester **8** through a conjugate-addition cyclization protocol previously reported from our laboratory.[11]

Scheme 2



The relative stereochemistry of the two stereogenic centers of acetylene **8** is vital to obtaining high levels of asymmetric induction in the photocycloaddition.[12] Since attempts to directly form the *anti* aldol product **10** using know protocols[13] resulted in either enolate decomposition or poor selectivity, a two step sequence based on Seebach's[14] precedent was investigated. Addition of the lithium enolate of ethyl acetate to acrolein at -78° C produced the hydroxy ester **9** in 99% yield. Exposure of **9** to 3 equivalents of LDA in THF followed by addition of propargyl bromide provided the desired *anti* aldol product **10** in 95% yield and >95% d.e.[15] The hydroxy ester **10** was then treated with 5 equivalents of methylmagnesium bromide to give 99% of diol **11**. Protection of the 1,3 diol as its acetonide with dimethoxypropane and PPTS in dichloromethane followed by carbomethoxylation of the terminal acetylene gave the acetylenic ester **8** in high yield. Ester **8** was treated according to the standard protocol[11] previously described (zinc homoenolate derived from **12**, $ZnCl_2$, ultrasound, CuBr-SMe_2, HMPA, 1:1 THF:Et_2O) for conversion to the 2-carbomethoxycyclopentenones **7** (83% yield). Irradiation of **7** in hexanes provided a single, isolable photoadduct **13**. The high diastereoselectivity for the photoaddition of **7** can be rationalized by molecular mechanics calculations of the two conformations **14a** and **14b**. The calculated energy difference closely approximates the experimentally observed product ratio. The synthesis provided access to exclusively the *anti* diastereomer **13** in seven steps from ethyl acetate in 50-55% overall yield.

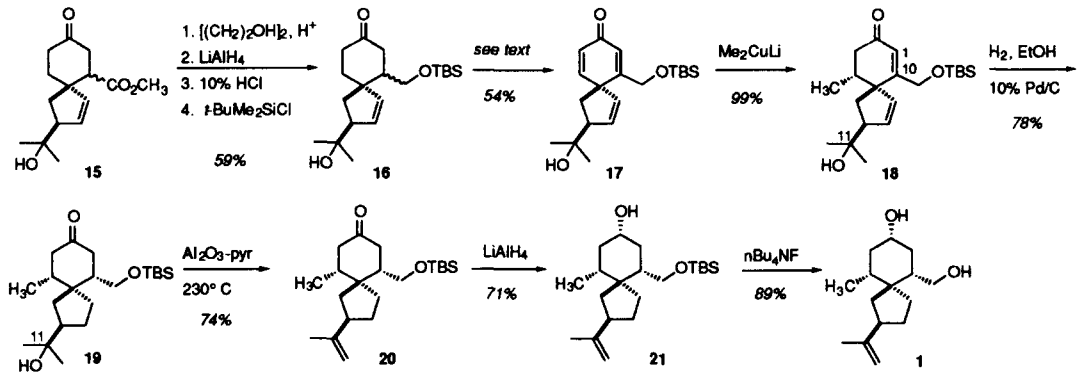


Completion of the synthesis required that the planned radical rearrangement be executed and that the product be refunctionalized to lubiminol. To this end, the photoadduct **13** was hydrolyzed and the secondary alcohol was selectively converted to its thiocarbamate **6** with 1,1'-thiocarbonyldiimidazole in THF at 65° C. Slow addition of tributyl tin hydride to thiocarbamate **6** over 5 - 6 hours produced a 3:2 mixture of the expected

rearrangement products **15** in 92% combined yield. The next goal was to introduce the C4 methyl group with the required stereochemistry. The keto esters **15** were converted to the TBS ethers **16** in high overall yield as shown in Scheme 3. Treatment of ketones **16** with sodium hydride and methyl phenylsulfinate[16] followed by heating the crude product in benzene gave a mixture of regioisomeric enones. The crude mixture of isomeric enones was then converted to the dieneone **17** via the selenides (LDA, PhSeCl, THF; $NaIO_4$, THF, H_2O). Exposure of the dienone **17** to lithium dimethyl cuprate in ether at -40° C produced a single diastereomer **18** in 99% yield.

Having introduced the C4 methyl with the required stereochemistry, it remained to reduce the two alkenes and the C2 carbonyl as well as dehydrate the tertiary hydroxyl at C11. The critical hydrogenation of the C1,10 alkene was accomplished with high stereoselectivity and concomitant reduction of the C6,7 alkene by catalytic reduction with hydrogen and palladium on carbon in acid free ethanol to give ketone **19**. Heating the tertiary alcohol **19** in the presence of pyridine on alumina[17,4] at 230° C resulted in regioselective dehydration of the tertiary alcohol to generate the isopropylidine **20**. Reduction of the C2 carbonyl was accomplished with lithium aluminum hydride to provide a 9:1 separable mixture of the equatorial:axial alcohols **21** respectively. Removal of the silyl protecting group with tetrabutyl ammonium fluoride completed the synthesis.

Scheme 3



A highly stereoselective synthesis of the hydroxylated spirovetivane lubiminol (**1**) has been accomplished. The synthesis is highlighted by a conjugate addition-cyclization to prepare the photosubstrate **7**, a diastereoselective intramolecular photoaddition to establish the C5-C7 relative stereochemistry and a radical fragmentation-rearrangement sequence to convert the photoadduct to the spiro [5.4] decane skeleton.

Acknowledgement: We thank the National Science Foundation (CHE 9014641) and the National Institute of General Medical Science (GM38904) for generous financial support.

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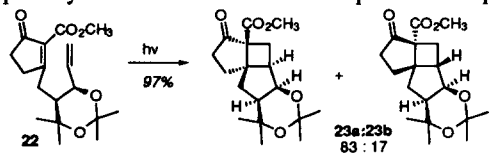
12. The corresponding *syn* diastereomer **22** provided an 83:17 mixture of diastereomers in the photocycloaddition. This ratio corresponds to that predicted by the molecular mechanics model.



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(*Received in USA* 11 *September* 1996; *accepted* 4 *October* 1996)