Pergamon

Tetrahedron Letters 39 (1998) 2443–2446

TETRAHEDRON LETTERS

Reactivity of 3-Oxo-15-hexadecanolide

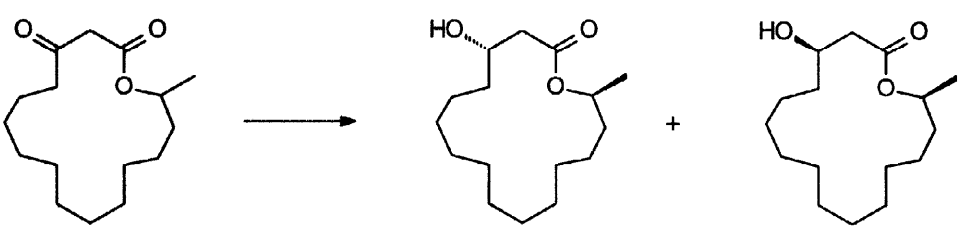
Anurag Sharadendu and Larry Weiler*

Department of Chemistry, University of British Columbia, Vancouver, British Columbia, CANADA V6T 1Z1

Received 22 October 1997; accepted 16 January 1998

Abstract: Reduction of 3-oxo-15-hexadecanolide (**1**) was carried out with high stereoselectivity and good chemical yield. The relative stereochemistry of the minor β-hydroxy lactone **3** was determined by X-ray crystallography. The dianion of **2** underwent stereoselective alkylation in modest yield. The relative stereochemistry of **6** was determined by chemical correlation and found to be consistent with the Frater model for such alkylations. Alcohol **6** was also available, in higher yield, by C-2 alkylation of **1** followed by reduction.

For some years we have been interested in the chemistry of relatively simple macrocyclic lactones, in particular, the 14-membered lactones that might provide some insight into the chemistry and activity of the 14-membered ring macrolide antibiotics.[1] For example, we have reported the synthesis, conformational analysis and reactivity of 14-membered β-keto lactones.[2] However, a number of macrolide antibiotics with a 16-membered ring β-hydroxy lactone skeleton have been isolated.[1] Very little is known about the reactivity of such systems.[3]



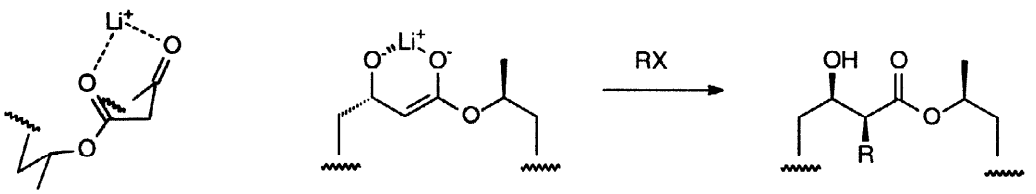
1 **2** **3**

The β-keto lactone **1** was prepared in 32% yield by a cyclization of the dianion[4] of (12'-bromo-2'-dodecyl)-3-oxobutanoate. Reduction of **1** using $NaBH_4$ gave a 2.5:1 ratio of the diastereomers in 88% yield. We were unable to separate these isomers. However, the C-3 multiplets were easily integrated in the ^{1}H-NMR spectrum of the mixture. It was not possible to directly determine the relative stereochemistry of the two diastereomers at this stage. However, the two alcohols were derivatized with 4-bromobenzenesulfonyl chloride to give the corresponding 4-bromobenzenesulfonates. Fortunately, these two diastereomers separated on silica. Furthermore,

0040-4039/98/$19.00
PII: S0040-4039(98)00236-6

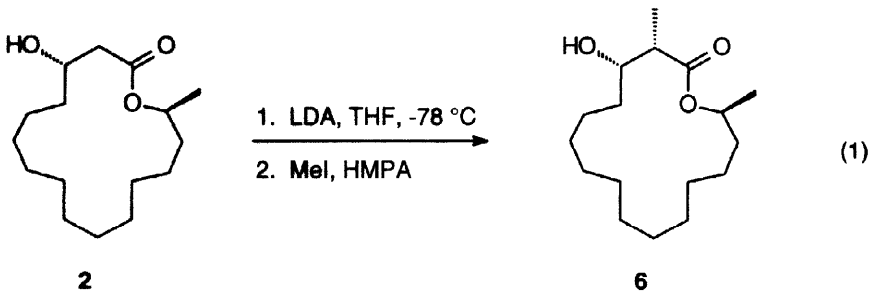
the minor isomer crystallized from hexane. These colourless crystals were suitable for an X-ray crystallographic study. This derivative was found to be the (3*R**,15*S**) isomer shown in **3**. Thus the major isomer in the reduction of **1** must have the (3*S**,15*S**) configuration as in **2**.

When L-Selectride [Li(*s*-Bu)$_3$BH] was used as reducing agent, only **2** was observed. However, only 50% of the product was obtained and 50% of the starting material was recovered. This ratio of product to starting material, as well as the stereoselectivity, was unaffected by changing the temperature, or the number of equivalents of L-Selectride used. These results led us to speculate that addition of L-Selectride resulted in two competing reactions: reduction and deprotonation of the C-2 methylene proton to give the enolate that did not undergo reduction. Other reducing agents, K-Selectride, LS-Selectride and lithium (diisobutyl)-(*n*-butyl)aluminium hydride[5] were also tried to improve the yields of reduction. They gave similar results to L-Selectride. However, when one equivalent of $NaBH_4$ was added after the initial addition of L-Selectride to β-keto lactone **1**, the alcohol **2** was isolated in 92% yield and none of the other diastereomer **3** could be detected. This is the same stereoselectivity we observed in the case of the analogous 14-membered lactone and suggested that a similar chelated transition state, such as **4**, can be used to rationalize the stereochemical outcome of this reaction.[2] Hydride attack from the si face of the keto group in **4** will result in the formation of the (3*S**,15*S**) product as observed.



4 **5**

Frater and Seebach have reported the highly stereoselective alkylations at C-2 in β-hydroxy esters via their corresponding dianions.[6] The major product **5** has the hydroxyl and alkyl groups anti to each other in this conformation. Previously we had extended this reaction to the macrocyclic lactone, (3*S**,13*S**)-3-hydroxy-13-tetradecanolide.[2] In the present study the dianion of the hydroxy lactone **2** was generated with slightly more than two equivalents of LDA. HMPA and methyl iodide were added and the reaction mixture was warmed after one hour and quenched (equation 1). The relative stereochemistry of C-3 and C-15 in **6** were already known and the third chiral center could be deduced on the rationale provided by Frater and Seebach.[6] However, we decided to unambiguously prove the relative stereochemistry at C-2.

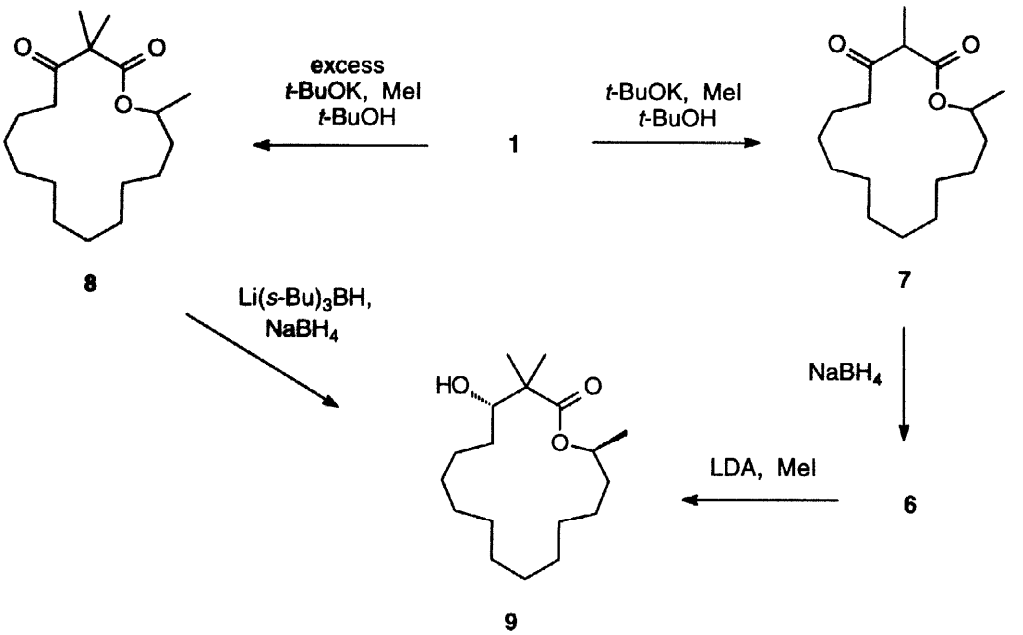


2 6 (1)

During earlier studies on the alkylation of 15-hexadecanolide, the two diastereomers of 2-methyl-15-hexadecanolide were synthesized and characterized.[7] As a result the secondary hydroxyl of **6** was converted into its thiocarbonate derivative and deoxygenated to the methylene group using a modification of the Barton-Jaszberenyi method employing tris(trimethylsilyl)silane as the reducing agent.[8] The ^{1}H NMR spectrum and chromatographic properties of the compound from **6** was identical to that of (2*S**,15*S**)-2-methyl-15-hexadecanolide. Hence, the stereochemistry of **6** was unambiguously assigned as (2*S**,3*S**,15*S**) where the 3-hydroxy and 2-methyl groups had the stereochemistry suggested by the Frater-Seebach mechanism for alkylation of open-chain β-hydroxy esters.

Although a very high stereoselectivity was observed in this alkylation of **2**, the reaction never went to completion and up to 50% starting material was often recovered, irrespective of the reaction conditions. To explore the reasons why this reaction did not go to completion, the dianion of β-hydroxy lactone **2** was quenched with D_2O. The ^{1}H NMR showed that this product had one full deuterium at C-2 carbon. Interestingly two diastereomers were produced in a 2:1 ratio by ^{2}H-NMR. Having demonstrated that the anion is formed and alkylated with high stereoselectivity, we are still unable to offer an explanation as to why the dianion alkylation of **2** does not go to completion.

Monoalkylation of **1** could be carried out in 65% yield to give **7** as a 2:1 mixture of C-2 epimers. Reduction of **7** with $NaBH_4$ gave an 85% yield of an alcohol identical with **6**. Thus equilibration of the C-2 isomers of **7** must be faster than reduction. The 2,2-dimethyl product **8** was prepared in 77% using excess base and MeI. Reduction of the β-keto lactone **8** with L-Selectride produced a single diastereomeric alcohol in good yield. This alcohol was identical to the product obtained from a second Frater alkylation of **6** and hence must have the stereochemistry shown in **9**. However, the L-Selectride reaction was very sluggish. Again this problem was circumvented by adding one equivalent of $NaBH_4$ to the reaction mixture 30 minutes after the addition of one equivalent of L-Selectride to **8**. Under these conditions **9** was isolated in 89% yield.



Thus we have been able to carry out stereoselective reductions and alkylations at C-2 and C-3 of 3-oxo-15-hexadecanolide and the model developed to rationalize the stereochemical outcome of these reactions paralleled our proposals for the 14-membered lactones suggesting that these models may have some generality.[9]

References and notes

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9. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support, to Professor J. Trotter and Dr. S. Rettig for the X-ray crystallographic structure determination, and Professor Clive for a very helpful suggestion.