Replicative Chirons: Stereoselective Synthesis of Oligo-Tetrahydrofuranic Lactones *via* C-Glycosylation with [(Trimethylsilyl)oxy]furan

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Natural oligo-tetrahydrofuranic compounds such as the antibiotic ionophores[1] and annonaceous acetogenins[2] are widely found from several natural sources. These compounds are of growing biological interest, particularly as cytotoxic, antitumor, or antiparasitic agents, due to their new mechanisms of action.[3] Indeed, they all show cytotoxicity ranging from 10^{-1} to 10^{-12} μg/mL, depending both on the cancerous cell lines tested and the structure.[2] However, poor specific cytotoxicity has been found for such products. Therefore, tremendous efforts toward the preparation of these bioactive products have appeared in the literature,[4] following different strategies dealing with the stereocontrolled elaboration of contiguous oxygenated five-membered heterocycles.[5,6] Most of these approaches are limited to the preparation of stereodefined units due to the origin of the starting material(s) and/or diastereoselective reactions used. Recently, Keinan's group has shown that a large number of diastereomers of a bis-tetrahydrofuranic butyrolactone, which can be used as key intermediate in the total synthesis of acetogenins of Annonaceae, could be obtained through cross-coupling reactions between chiral aldehydes and chiral phosphorus ylides, followed by a Kennedy oxidation−Williamson cyclization sequence.[7] In this paper, we report that stereomers of these bis-tetrahydrofuranic butyrolactones may be stereoselectively obtained by replicative C-glycosylation of anomeric acetoxytetrahydrofurans with [(trimethylsilyl)oxy]furan (TMSOF). The advantage of this approach is that it can also be used to build up tris-tetrahydrofuranic butyrolactones as well as to prepare natural acetogenins.

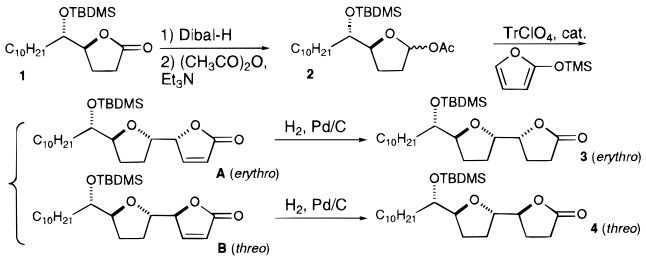

Figure 1.

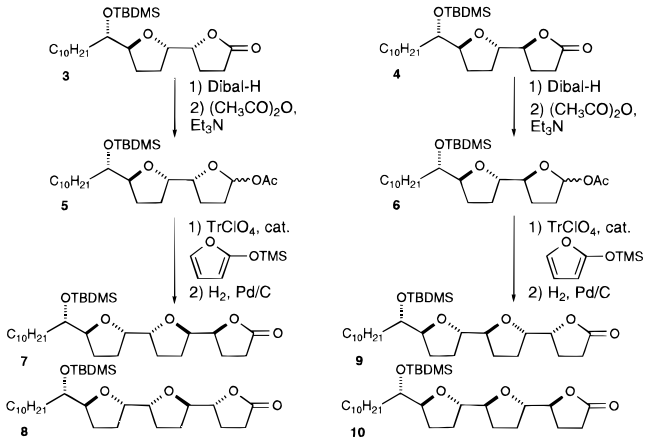

Figure 2.

Starting from the protected silyl ether of (−)-*nor*-muricatacin **1**, (4*S*,5*S*)-5-hydroxy-4-pentadecanolide, which has been prepared in five steps from L-glutamic acid,[8] the corresponding acetoxy derivatives **2** were prepared by reduction of **1** with DIBAL-H at −78 °C in toluene (96%), followed by treatment with 10 equiv of acetic anhydride in the presence of triethylamine at room temperature (92%). Then, addition at 0 °C in anhydrous diethyl ether to the so obtained mixture of the anomeric acetates **2**, of 1 equiv of TMSOF, in the presence of 10% molar of trityl perchlorate ($TrClO_4$), afforded a separable mixture of only *two* adducts, namely the *erythro-trans* and *threo-trans* desired butenolides **A** and **B** in 92% yields and 60:40 diastereomeric ratio (in favor of the *erythro* compound **A**)[9a] (Figure 1). Use of different Lewis acids and/or reaction conditions did not improve this result. However, treatment of either diastereomer with triethylamine led to the identical mixture of butenolides in the same ratio (60:40), through epimerization at C-4. The stereoselectivity of the reaction so observed may be rationalized by stereodifferentiation of one face of the intermediate cyclic oxonium ion due to the steric hindrance of the long alkyl chain, whereas the low facial differentiation of the nucleophile is probably a result of a thermodynamic equilibrium between both products, as shown by the epimerization experiment.

After separation by flash chromatography, the two butenolides **A** and **B** were independently and quantitatively hydrogenated over palladium on charcoal in toluene to lead to the desired butyrolactones **3**, and **4**. The stereochemical relationships of the two diastereomers were determined by NMR studies both on the butenolides and their saturated analogues and confirmed both by

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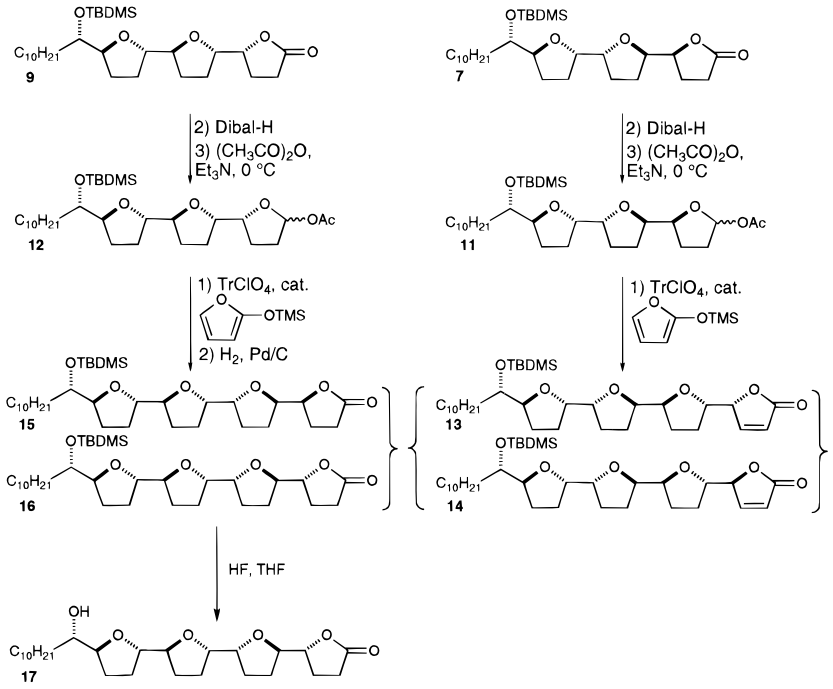

Figure 3.

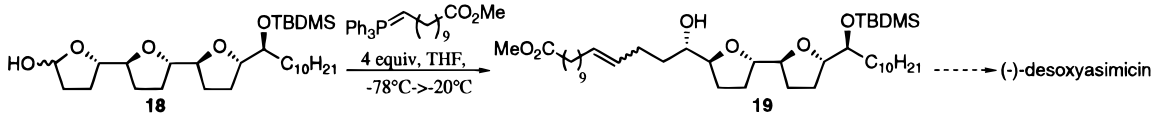

Figure 4.

chemical correlation through an alternative and stereospecific synthesis of **4**[9a] and comparison of the spectroscopic data of **4** with Keinan's products.[7b] These substrates were then separately used in a second sequence, namely the reduction−acetylation−C-glycosylation−hydrogenation transformations using the same reagents and reaction conditions as described above (70% overall yield for the four steps), in order to obtain the corresponding lactones **7**−**10** possessing an extra tetrahydrofuran ring (Figure 2).

It is noteworthy that after the second C-glycosylations only two adducts (among the four possible) are formed, which possess the *erythro-trans* and *threo-trans* stereochemical relationships across the butenolide−tetrahydrofuran pattern. Yields and diastereomeric ratios are comparable to the former values obtained in the initial sequence (85% combined chemical yield and dr = 60:40 in favor of the *erythro* compound). The stereoselectivity of the reaction may be rationalized again by invoking the same effects as those described above. The stereomers are easily separated by flash chromatography and may be used, after hydrogenation, as starting material for the same sequence. For instance, **7** and **9** were separately used in a new reduction−acetylation−C-glycosylation sequence (Figure 3).

The expected adducts were obtained in a 60:40 ratio in favor of the *erythro* compound but in a lower yield (60%). After hydrogenation, compound **16** was treated with HF for removal of the protecting group to yield alcohol **17** in 92% overall yield for the last two steps.

Even though we did not extend this methodology to the preparation of tetrakis-tetrahydrofuranic butyrolactones, this strategy is probably not limited to the preparation of the tris-tetrahydrofuranic butyrolactones and could be extended to the synthesis of oligo-tetrahydrofuranic butyrolactones as well.

It is noteworthy that theoretically this sequence could also be used with substituted TMSOF derivatives, leading after hydrogenation of the butenolides so obtained, to 3,4-disubstituted tetrahydrofurans. Consequently, by combining the different synthons, libraries of oligo-tetrahydrofuranic butyrolactones may be thus obtained. Indeed, because of the high cytotoxicity observed with the natural acetogenins of Annonaceae, structurally related analogues should be designed and synthesized in order to obtain more specific chemotherapeutic agents.

In the annonaceous acetogenins field, we have used compound **18** as a key building block for the preparation of the C1−C34 fragment of natural deoxyasimicin. Indeed, lactone **10** after reduction by DIBAL-H at −78 °C led to the corresponding lactol **18** (94%), which can then be treated with 1 equiv of the required phosphorus ylide in the presence of potassium *tert*-butanolate to afford, *via* a Wittig homologation, the desired ethylenic coupled product **19** (Figure 4). Then this product will lead through known procedures[10] to the natural product deoxyasimicin.[2]

In conclusion, the very efficient C-glycosylation of cyclic oxonium ions with TMSOF allows a straightforward access to oligo-tetrahydrofurans, due to this excellent stereoselective and high-yielding reaction. The mild reaction conditions allow one to prepare a large variety of oligo-tetrahydrofuranic butyrolactones that can lead to more elaborate compounds such as the acetogenins of Annonaceae.

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Supporting Information Available: Physical data of compounds **1**−**19** (10 pages).

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