

Synthesis of Bis-THF Compounds from D-Glucose

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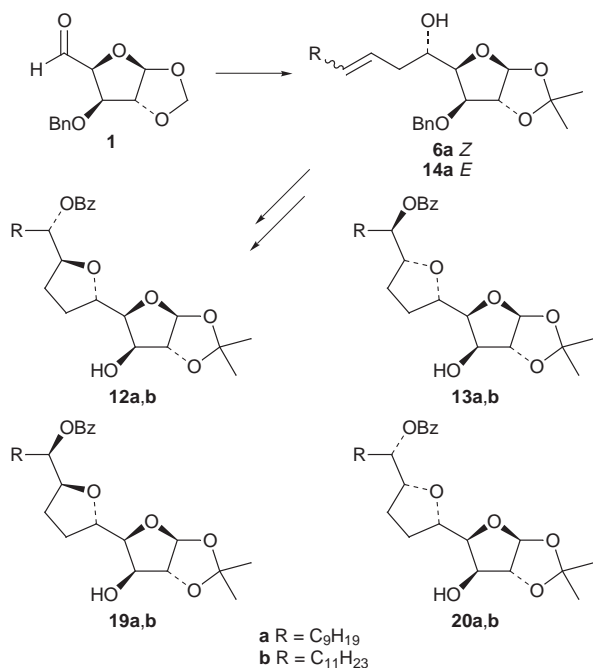
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Starting from diacetone-D-glucose, four diastereomeric bis-THF compounds related to annonaceous acetogenins are prepared using two strategies.

Nearly 300 annonaceous acetogenins, some of them possessing potent biological activity (cytotoxic, pesticidal, etc.), have been isolated in the past decade.^{1,2} The presence of one to three tetrahydrofuran (THF) ring(s), either adjacent or not, and a terminal lactone moiety are characteristic of these compounds. Some of the most active acetogenins, such as bullatacin,² have two adjacent THF rings with *erythro* or *threo* configuration for the side chain. Thus, the synthesis of enantiopure bis-THF synthons from readily available carbohydrates, such as D-glucose, has been studied.⁶ The presence of added functions (OH, OR) in one THF ring may be of interest, since it has been postulated that these rings are located at the polar surface of the cell membrane, the terminal side chain and the lactone moiety being embedded in the lipidic layer of the membrane.⁵ Two strategies have been used starting from aldehyde **1**.⁷ Either introduction of an unsaturated terminal side chain followed by epoxidation–cyclisation (Scheme 1) or preparation of a bis-THF aldehyde followed by

hydrogenolysis and separation by flash chromatography (30% overall yield for each). Relative configurations were determined by ¹H NMR spectroscopy according to the Cassidy model.¹¹ Starting from 1-bromobut-3-ene, a 1 : 1 mixture of epimeric alcohol **21a** led, under Swern conditions, to an unexpected 2 : 1 mixture of aldehydes **24** and **25** (readily epimerized to a thermodynamic 1 : 1 ratio with Et₃N). Addition of C₁₂H₂₅MgBr to the latter afforded **12b**, **13b** and **19b** in a ratio of 25 : 27 : 48 (after benzylation, hydrogenolysis and chromatographic separation) in accord with a fast epimerisation of the starting aldehydes. As above, Swern oxidation of a 1 : 1 mixture of secondary alcohols gave ketones **26** and **27** in a 2 : 1 ratio. These ketones were reduced by L-Selectride or NaBH₄ with different diastereoselectivities (epimerization of ketones was observed with the latter) in agreement with literature data^{15,12b} (Table 2).

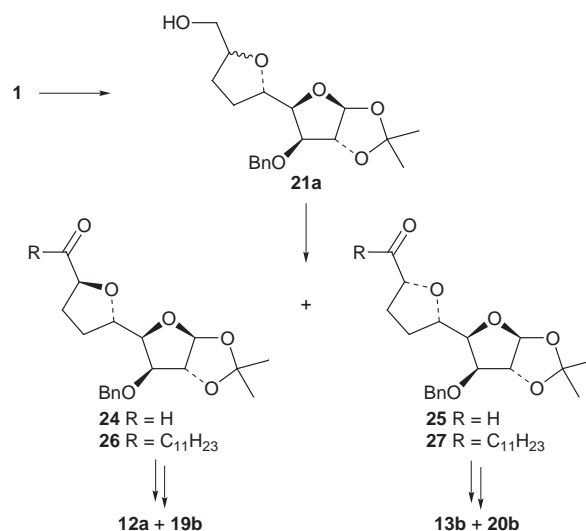


Scheme 1

Grignard reaction and product interconversion *via* oxidation–reduction (Scheme 2). The four possible diastereoisomers **12a**, **13a** and **19a**, **20a** were respectively obtained from the 5*S* alcohols **6a** (*Z*) and **14a** (*E*) after epoxidation–cyclisation (*m*CPBA, AcOH), benzylation,

Table 2 Relative percentage of alcohols obtained from reduction of ketones **26/27**

Alcohol	12b	13b	19b	20b
L-Selectride [©]	63	23	–	14
NaBH ₄	22	11	34	33



Scheme 2

In conclusion, four diastereoisomeric enantiopure bis-THF compounds related to annonaceous acetogenins have been prepared from D-glucose. Further elaboration towards new acetogenin analogs is anticipated through chain extension at C-1.

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Techniques used: IR, ^1H and ^{13}C NMR, MS and HRMS, polarimetry

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Schemes: 7

Figure: 1

Tables: 2

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