The Total Synthesis of Litsenolides C_1 and C_2

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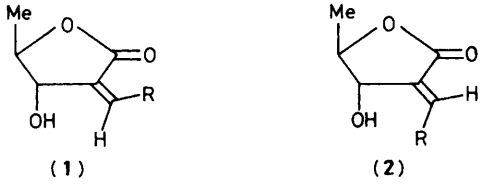
Naturally occurring α-alkylidene-γ-butyrolactones can be prepared from a carbohydrate precursor using Wittig methodology to form the exocyclic double bond.

The α-alkylidene-γ-butyrolactone building block is found in a huge range of natural products, and is thought to be responsible for many different types of biological activity. Compounds containing the grouping have been reported to have anti-tumour, cytotoxic, phytotoxic, and antimicrobial activities, and to cause allergic contact dermatitis. These activities are thought to be due to the compounds acting as Michael acceptors for biological nucleophiles such as L-cysteine or thiol-containing enzymes.[1]

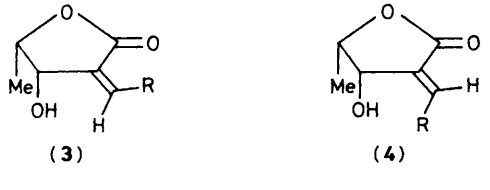
Among the more simple compounds in the class are the litsenolides [(**1**) and (**2**)] and dihydromahubalactones [(**3**)–(**6**)], which have been isolated from the roots of the Japanese shrub *Litsea japonica* and the trunk wood of the Amazonian 'Mahuba' tree (*Clinostemon mahuba*) respectively.[2,3] Two general strategies have been adopted in the synthesis of these compounds: lactonization of a long-chain acid or its equivalent,[4] and α-functionalization of a preformed γ-butyrolactone ring.[5] In the latter case there has been no reported attempt to use Wittig methodology to form the exocyclic double bond, despite the obvious advantages the procedure would have in terms of the variety of alkylidene groups which could be introduced. Presumably the reluctance to adopt Wittig chemistry in this case is due to the highly reactive nature of ketones located α to electron-withdrawing groups. We report herein the successful synthesis of optically pure litsenolides C_1 (**1c**) and C_2 (**2c**) using D-glucose as starting material and a Wittig reaction to form the exocyclic double bond.

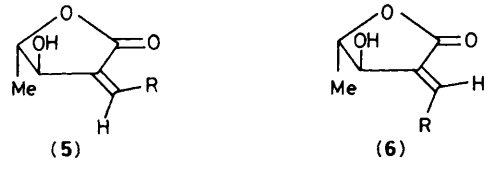
The synthetic route (Scheme 1) was designed such that the Wittig reaction was carried out at a late stage in the synthesis, in order to increase the generality of the approach. Thus the ketone (**12**) would be the substrate for the Wittig reaction and the different C-2 substituents found in the natural products could be introduced by changing the Wittig reagent.

The first task in the synthesis was to establish the correct stereochemistry at C-3 and the correct chain length and oxidation level at C-4 of the starting material.† Inversion at

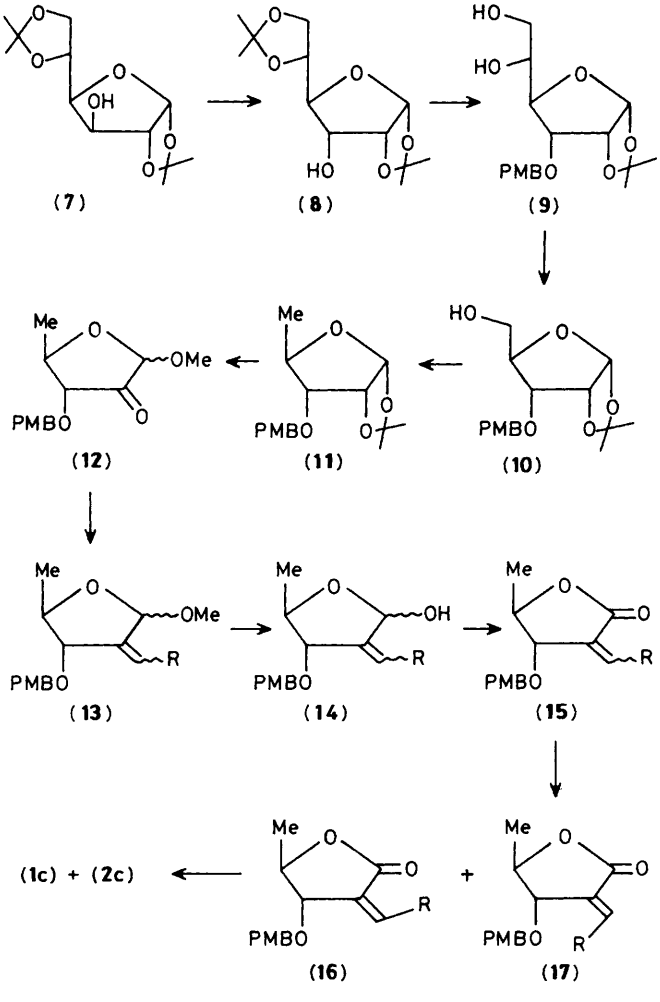


a; R = $[CH_2]_9CH{=}CH_2$
b; R = $[CH_2]_9C{\equiv}CH$
c; R = $[CH_2]_{11}CH_2Me$





a; R = $[CH_2]_{13}CH{=}CH_2$
b; R = $[CH_2]_{13}C{\equiv}CH$
c; R = $[CH_2]_{13}CH_2Me$



Scheme 1. PMB = *p*-methoxybenzyl.

† Carbohydrate numbering is used throughout.

C-3 of (**7**) by oxidation (Me_2SO, Ac_2O) and reduction ($NaBH_4$; overall yield 60% after chromatography) is well known,[6] but use of catalytic RuO_4 oxidation[7] followed by reduction ($NaBH_4$) was found to be more efficient (60% yield, no chromatography required). From (**8**), the C-3 hydroxy group was protected as a *p*-methoxybenzyl ether‡ [NaH, *p*-$MeOC_6H_4CH_2Cl$, tetrahydrofuran (THF)][8] and the 5,6-isopropylidene group was removed by hydrolysis, under standard conditions (0.8% H_2SO_4),[9] to give (**9**).

In order to provide the C-4 methyl group of the target, the 5,6-diol unit of (**9**) was sequentially cleaved and reduced in a one-pot process [$NaIO_4$, MeOH–H_2O; $NaBH_4$, 93% yield of (**10**) from (**8**)]. The primary hydroxy group was then reduced by methanesulphonylation ($MeSO_2$, pyridine) and reduction [$LiAlH_4$, 88% from (**10**)], leading to (**11**).

Having established and protected the required functionality at the two chiral centres, we turned to the crucial section of the synthesis: conversion of C-1 and C-2 into the α-alkylidene lactone function. The required ketone was prepared by methanolysis of (**11**) to give a mixture of anomers (10 : 1, β : α) and oxidation (Me_2SO, Ac_2O) to give first the hydrate of (**12**) and then the ketone [94% from (**11**)] itself after dehydration (3 Å molecular sieves, CH_2Cl_2) and the first column chromatography of the synthesis.

The crucial Wittig reaction was next attempted using (**18**) as the reagent. Previous attempts to use Wittig reactions in the preparation of α-methylene-β-butyrolactones (rather than α-alkylidene-β-butyrolactones) from C-2 keto furanosides have been characterized by two problems. First the yield of the alkene has been poor,[10,11] although results in the pyranoside series have been more encouraging,[12] and secondly hydrolysis of the anomeric protection after introduction of the exocyclic double bond has led to the formation of furans.[10] Neither of these problems was encountered in this synthesis. Thus treatment of (**12**) with Bu^nLi and (**18**) in THF gave (**13**) in 69% yield as a mixture of geometric isomers. The anomeric protection was then easily removed (THF–H_2O, HCl, quantitative) leading to a 1 : 1 mixture of (**14**) and the corresponding hydroxy-aldehyde. Oxidation with Fetizon's reagent (Ag_2CO_3–Celite, C_6H_6, 92%)[13] gave (**15**) which could be deprotected under standard conditions [2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), CH_2Cl_2–H_2O][9] to give a mixture of (**1c**) and (**2c**) in 3 : 1 ratio.

‡ All new compounds had satisfactory chemical analyses and spectroscopic characteristics.

In order to provide pure samples of (**1c**) and (**2c**), the mixture of geometric isomers (**15**) was separated by flash chromatography and the products (**16**) and (**17**) were then separately deprotected. The synthetic litsenolides C_1 and C_2 thus obtained had identical physical and spectroscopic properties to those reported for the naturally occurring compounds. The overall yield of the sequence was 12%. With a successful method for the preparation of the α-alkylidene lactone moiety of the target compounds, further work is in hand to exploit the technique in the synthesis of the mahubalactones and other, more complex, naturally occurring α-alkylidene-β-butyrolactones. The way is also open for the preparation of unnatural analogues of this important class of compound.

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