# The Synthesis of the Dihydromahubanolides

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Two epimeric, naturally occurring α-alkylidene-γ-butyrolactones have been prepared from a carbohydrate precursor, using a Wittig reaction to form an exocyclic double bond either with or without epimerisation at the centre α to the olefin, depending on the reaction conditions employed.

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] We recently reported the total synthesis of optically pure litsenolides $C_1$ **1c** and $C_2$ **2c**, using D-glucose as a starting material.[4,5] A central feature of these syntheses was the use of a Wittig reaction on a C-2 keto-sugar. We now wish to report the total syntheses of isodihydromahubanolide A **6c** and dihydro- and isodihydro-mahubanolides B **3c** and **4c**, in which we have extended and developed the chemistry used in our earlier syntheses.[6]

The syntheses of both dihydro- and isodihydro-mahubanolides A and B (Scheme 1) started from the mesylate **7**, an

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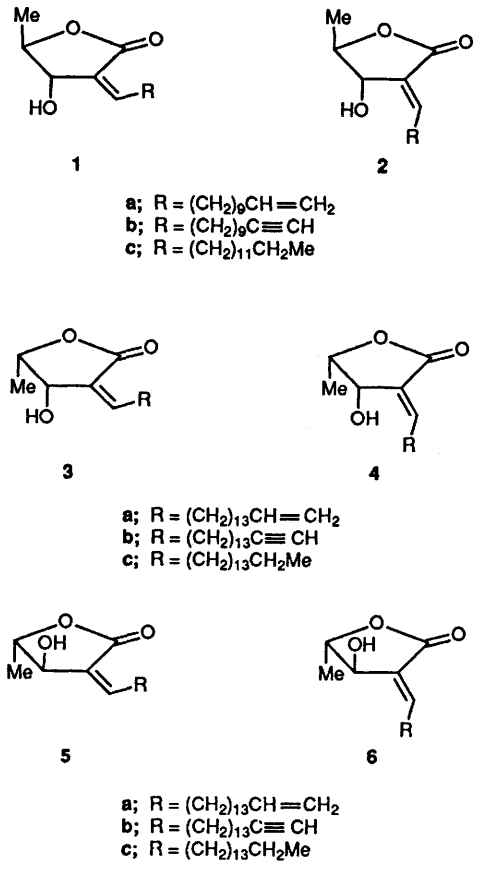


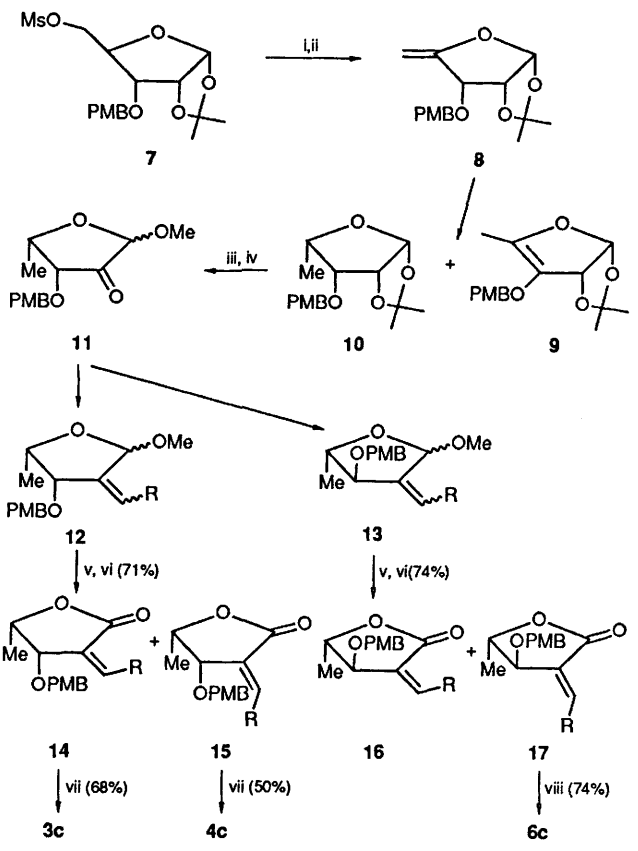


**Scheme 1.** *Reagents and conditions:* i, KI, MeCOEt (reaction yield 89%); ii, KOBu$^t$, THF, 0 °C (97%); iii, MeOH, HCl (80%); iv, DMSO, $Ac_2O$ (quant.); v, THF, $H_2O$, HCl (quant.); vi, Fetizon's Reagent; vii, DDQ, $CH_2Cl_2$, $H_2O$.

intermediate in our previous work. The first task in the synthesis was to invert the stereochemistry at C-4 by elimination and hydrogenation. This was achieved by formation of an iodide and elimination of the elements of hydrogen iodide to give the enol ether **8**, which decomposed slowly at room temperature. Hydrogenation of **8** (Pd–C, ethyl acetate) gave two products which were identified as the saturated compound **10**, with the desired stereochemistry at C-4, and the rearranged olefin **9**. While the rearranged olefin **9** could be hydrogenated under more forcing conditions to give mostly **10**, some cleavage of the *p*-methoxybenzyl ether occurred.

The rearrangement of olefins under the influence of palladium catalysts is well-documented, as is the tendency of rhodium catalysts to prevent the process.[7] It has also been reported that rhodium on alumina does not cause cleavage of *p*-methoxybenzyl ethers.[8] Hydrogenation of **8** over rhodium on alumina gave the required xylofuranose **10** in excellent yield (98%) after 4 h, with no trace of the rearranged product. Interestingly, further hydrogenation did take place if the reaction was left for more than 4 h, leading to saturation of the aromatic ring of the *p*-methoxybenzyl ether.[9]

With a ready supply of **10** available, we turned our attention to the conversion of the 1,2-acetonide into the α-alkylidenone moiety of the target. The ketones **11** were prepared as detailed in Scheme 1. In our earliest studies,[5] we had found that furanose C-2 ketones underwent smooth Wittig olefination at low temperature, however in that instance the methyl group at C-4 and the *p*-methoxybenzyl ether at C-3 were *trans* to each other and so there was little driving force for epimerization at C-3. When **11** was subjected to the same Wittig conditions, followed by deprotection at the anomeric position and oxidation with Fetizon's reagent, we obtained a mixture of products arising from scrambling of the stereochemistry at C-3.

At this stage we realised that, if we could control the stereochemical changes at C-3 and obtain either complete or no epimerisation at C-3 we would be able to synthesise both dihydro- and isodihydro-mahubanolides A and B from a common intermediate. After considerable experimentation, examining different bases, addition sequences and reaction temperatures, we found that generation of the ylide using n-butyllithium and very slow addition of this ylide to a cooled (−70 °C) solution of the ketone gave the unepimerised alkenes **12** in 73% yield.† On the other hand addition of the ketone **11** to a chilled (−70 °C) solution of the ylide resulted in a 79% yield of the completely epimerised alkenes **13**.‡ Although the literature abounds with examples of sensitive ketones which have undergone epimerisation during a Wittig reaction and other, apparently equally sensitive substrates which have retained their stereochemical integrity during the reaction, we believe that this is the first example in which both possible epimers have been obtained in apparently complete diastereoselective excess by relatively simple variations in the reaction conditions.

The syntheses of dihydromahubanolide B **4c**, isodihydro-

† n-Hexadecyltriphenylphosphonium bromide (2.3 mmol) was dissolved in dry THF and treated with n-butyllithium (2.5 mol $dm^{-3}$, 2.16 mmol). The ylide so formed was added dropwise over 40 min to **11** (1.5 mmol) at −70 °C and the reaction was worked up in the usual way after 2 h.

‡ KOBu$^t$ (3.1 mmol) was added to n-hexadecyltriphenylphosphonium bromide (3.1 mmol) in THF and cooled to −70 °C. Compound **11** (2.1 mmol) in THF was added dropwise over 20 min and the reaction worked up in the usual way after 2 h.

mahubanolide B **3c**, and dihydromahubanolide A **6c** were completed as indicated in Scheme 1. The synthesis of dihydromahubanolide A **5c** was terminated at the protected compound **16** as unsufficient material was available to warrant completion of the synthesis. All three of the natural products synthesised exhibited physical and spectral characteristics identical to those reported in the literature.[3]

In conclusion, we have successfully completed the syntheses of three of the dihydromahubanolides, employing a Wittig reaction at C-2 of a furanose carbohydrate in which the stereochemistry at the α-position (C-3) can be controlled at will to give either total or no epimerisation. We believe that this is the first example of such control.

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