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Synthesis of (+)-goniothalesdiol and (+)-7-*epi*-goniothalesdiol

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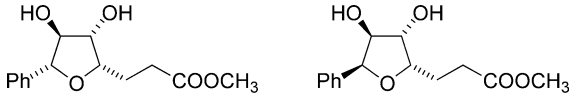
Dedicated to Prof. Peter Stanetty on his 60th birthday.

Abstract—A total synthesis of (+)-goniothalesdiol, a 3,4-dihydroxy-2,5-disubstituted tetrahydrofuran isolated from *Goniothalamus borneensis* (Annonaceae), and its 7-epimer is reported using oxycarbonylation methodology for construction of polyhydroxylated substituted heterocycles. Diastereoselectivity of addition of organometallic reagents to 2,3-*O*-isopropylidene-D-threose derivatives using theoretical calculations based on the semiempirical PM5 was studied.

1. Introduction

The palladium(II)-catalysed oxycarbonylation[1] of unsaturated polyols[2] or/and aminopolyols[3] represents a powerful methodology[4] for construction of 5-/6-membered saturated oxa/azaheterocycles. In our long term program directed towards the application of carbonylation methodology to natural product synthesis, we have described the syntheses of both enantiomers of cytotoxic styryl-lactones goniofufurone,[5a,b] 7-*epi*-goniofufurone,[5a,b] erythro-skyrine,[5c] homo-DLX,[5d] homo-DMDP,[5d] homo-DNJ[5e,f] and homo-L-ido-DNJ.[5e,f] Herein, we report experimental details of the optimised synthesis of goniothalesdiol **1** and 7-*epi*-goniothalesdiol **2** (Fig. 1) starting with D-mannitol.[6]



1 **2**

Figure 1. Goniothalesdiol **1** and 7-*epi*-goniothalesdiol **2**.

Goniothalesdiol was isolated from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae), and has been revealed to have significant cytotoxicity against P388 mouse leukaemia cells, and insecticidal activities.[7] The structure and relative stereochemistry of **1** was assigned on the basis of ^{1}H, ^{13}C NMR spectroscopy and the absolute configuration was confirmed by semi-synthesis from natural (+)-goniothalenol (altholactone).

Meanwhile, growing attention is given to this class of compounds, as demonstrated by development of new syntheses of unnatural enantiomer of goniothalesdiol (−)-**1**,[8] and its 7-epimer (+)-**2**.[9] Both syntheses started from chiral pool, D-glucuronolactone or D-tartaric acid, respectively, using Grignard addition followed by Lewis acid promoted hydrogenation of the corresponding lactone, the latter setting the *cis* configuration at C_6-C_7 of the epimer, and thus were not applicable for natural goniothalesdiol. Recently, preparation of 3,6-anhydro-2-deoxy-6-*C*-phenyl-D-*gluco*-1,4-hexonolactone **9**, an intermediate in our synthetic route,[6] was described from an erythrulose derivate[10] via an aldol reaction.

2. Results and discussion

We report herein details of the optimised synthesis[6] of natural goniothalesdiol (+)-**1** and its 7-epimer (+)-**2**. The strategy followed is shown in Scheme 1. In both routes the phenyl moiety is introduced by diastereoselective addition of organometallic reagents at C_1 of the aldose **6**, to allow for an entry into both diastereomers. For the second crucial step, oxycarbonylating bicyclisation of pentenitols, advantage is taken of recent progress in Pd(II)-catalysed carbonylations of unsaturated polyols or aminopolyols, that have turned out bicyclic lactones/lactams with high regio-control and excellent stereoselectivity, without necessity of OH-protection.[4,5]

Keywords: Palladium(II) catalysis; Stereoselective oxycarbonylation; Diastereoselective addition to carbonyl; Goniothalesdiol; Natural products; PM5 calculations.
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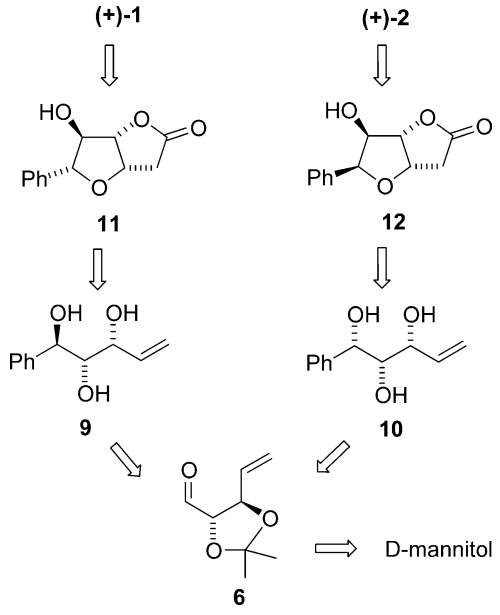
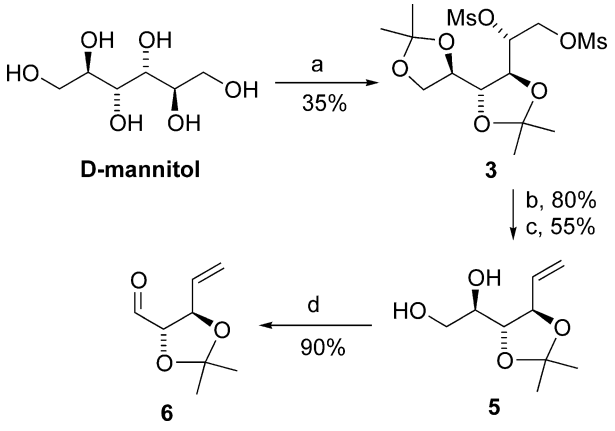


Scheme 1. Retrosynthetic analysis of **1** and **2**.

The first key intermediate, aldose **6**, was obtained from D-mannitol by a standard carbohydrate chemistry procedure.[11,12] Following the reaction sequence, acetonisation of D-mannitol,[13] selective hydrolysis of the terminal acetonide,[13] *O*-mesylation of both unprotected hydroxyl groups, reductive elimination with sodium iodide[14] and subsequent selective hydrolysis of the next terminal acetonide with HCl in ethanol, the diol **5** was readily prepared, however, in poor yield (3% overall[4a,6]).

In order to improve the efficiency of the synthesis of the requisite aldose **6** various reaction conditions for dioxolane ring hydrolysis and work up of reactions were examined. An effort that culminated in development of a four-step protocol for synthesis of C_5-aldose **6** with 14% yield, starting from cheap D-mannitol. (Scheme 2). The major improvement is the one pot conversion of D-mannitol to bismesylate **3**, which was isolated by simple crystallisation in 35% yield together with 30% of tris-*O*-acetonide-D-mannitol; the latter can be recycled. A selective hydrolysis

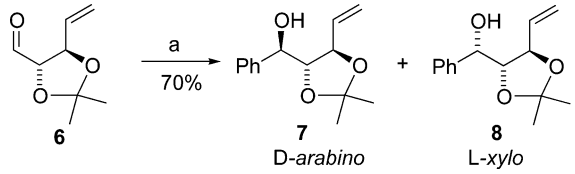


Scheme 2. Reagents and conditions: (a) 1, H_2SO_4, acetone; 2, H_2O; 3, NaOH; 4, MsCl, pyridine; (b) Lit.[14] NaI, acetone; (c) Lit.[15] $Zn(NO_3)_2 \cdot 6H_2O$, acetonitrile; (d) $NaIO_4$, H_2O.

of the second terminal acetonide was achieved with $Zn(NO_3)_2 \cdot 6H_2O$ in acetonitrile.[15]

With aldose **6** in our hands the synthesis was set up for the first key reaction of the sequence—Grignard addition with phenylmagnesium bromide (Scheme 3). A diastereomeric mixture of D-*arabino* **7** and L-*xylo* **8** partially protected pentenitols in the ratio 50:50 and 70% yield was obtained. The diastereomers could be readily separated by flash chromatography.

The unexpected lack of diastereocontrol observed in the



Scheme 3. Reagents and conditions: (a) PhMgBr, THF.

addition led us to study the reactions of organometallic reagents with aldehyde **6** in more detail.[16]

Generally, the design of addition of *C*-nucleophiles to aldehyde **6** could be based on models of either chelation-control: 1,2- (Cram) versus 1,3-asymmetric induction (Reetz) or non-chelation-control (Felkin-Anh), leading to alcohols **8** (1,2-*syn*, Cram) or **7** (1,2-*anti*, Reetz and Felkin-Anh).

Table 1 summarises the results of a series of micro scale experiments with several organometallics. The best results were noted with the Seebach reagent (entry 6, non-chelation control) and with $PhCeCl_2$ in diethyl ether at $-10\,^{\circ}C$, affording the requisite D-*arabino* diastereomer (1,2-*anti*) in 62% de (entry 1, chelation control). General *anti*-diastereoselectivity, observed in this set of reactions, in concert with literary references,[16] called for a new model of the transition state for these reactions. In the case of hard Lewis acids, such as $MgBr_2$ (entry 4), the convenient Cram's chelating model favored 1,2-*syn*-diastereomer (L-*xylo*, **8**), whereas dominance of 1,2-*anti*-diastereomer was found in practice. Our model considers a 1,2-chelation of the subsidiary Lewis acid along with the chelation of organometallic reagent, causing the *Re* face of carbonyl group to be the preferred one for a nucleophilic attack (model B, Fig. 2). The activation energy for this model of TS (model B, 4 kcal/mol), was considerably lower, than that predicted by the modified Cram's model (model A, ~8 kcal/mol) or classical Cram's model (15 kcal/mol). Transition state candidates were determined using saddle-point calculations and potential energy surfaces. PM5 semiempirical method was chosen as well balanced compromise between speed and accurancy,[17] even though it is still a novelty in the field of metal complex calculations.[18] Transition states were subsequently verified by vibrational and IRC analysis.

Predictions made by the suggested bis-chelation model of the transition state for addition of organometallic reagents to 2,3-*O*-isopropylidene-D-threose derivatives matched the