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Synthesis of polyhydroxylated bicyclic tetrahydrofurans and tetrahydropyrans via a stereoselective domino cyclization/reduction reaction

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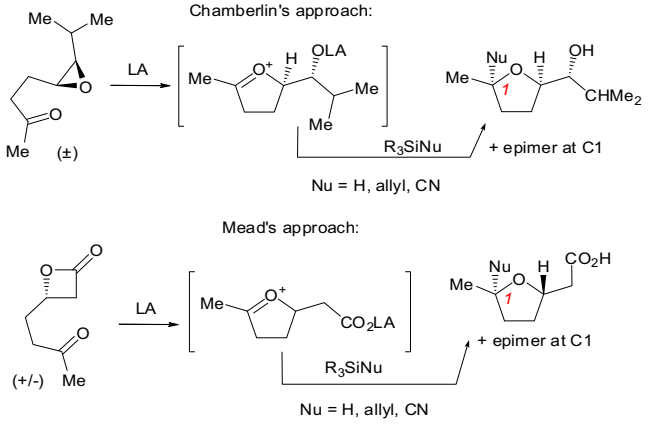
ABSTRACT

A novel reaction cascade involving a Lewis acid-induced migration of an isopropylidene protecting group followed by the formation of a pyranose or furanose ring and subsequent reduction of the hemiacetal is described. Depending on the reaction conditions, as well as, the stereochemistry of the substrate, polyhydroxylated tetrahydrofurans or tetrahydropyrans can be obtained in reasonable yields. The synthons used in this transformation were prepared via a highly stereoselective one-pot tandem reaction, consisting of a 1,4-Michael addition of vinylmagnesium bromide to D-glucose-derived cyclohexenone followed by aldol reaction with 2,3-*O*-isopropylidene-D-glyceraldehyde.

1. Introduction

One of the main challenges of modern organic synthesis consists of the planning and execution of transformations, which rapidly increase the molecular complexity. The most elegant examples are the domino processes, which according to a widely accepted definition, involve at least two consecutive reactions occurring under the same conditions without any reagents or catalysts being added during the course of the transformation.[1] Such approaches are very elegant and appealing to chemists, since they can also significantly shorten the synthesis and lower the total cost.

Among the wide range of domino processes discovered so far, reactions that give enantiomerically pure products, which often show significant biological activity are particularly important.[2] The stereocontrolled synthesis of substituted tetrahydrofuran and tetrahydropyran systems seems to be of great interest,[3] since such units are continuously encountered in natural products, e.g., polyether antibiotics[4] or acetogenins.[5] Several approaches leading to products with THF and THP scaffolds involve a Lewis acid-induced formation of cyclic oxacarbenium cation and its subsequent in situ reaction with a silicon-based nucleophile. Chamberlin et al. proposed a process utilizing epoxyketones,[6] whereas Mead et al. focused on a reductive cyclization of keto-β-lactones (Scheme 1).[7] Romo et al. took advantage of the latter approach, but utilized the tandem Mukaiyama aldol-lactonization reaction in order to obtain keto-β-lactones, which then in situ underwent a Mead-type process.[8]



Scheme 1. Domino approaches to THF derivatives developed by Chemberlin and Mead (*cis* products prevailing). Both groups proposed also analogical pathways for the synthesis of THPS.

Herein we report a novel stereoselective domino transformation involving an intramolecular migration of an isopropylidene unit induced by a Lewis acid, followed by a ring closure of the resulting hemiketal and its further reduction with triethylsilane. Depending on the stereochemistry of the substrate and the

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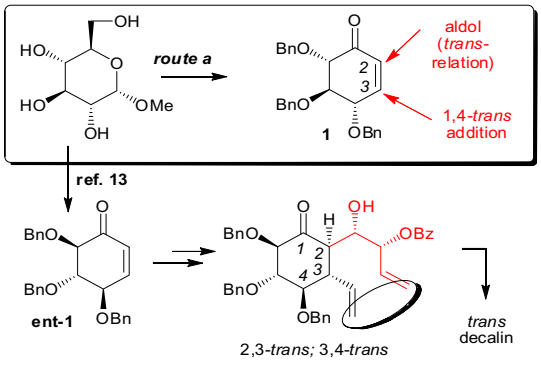
reaction conditions, different enantiomerically pure bicyclic polyhydroxylated THF and THP derivatives can be prepared. Such compounds may be regarded as conformationally locked carbasugars, which might act as sugar mimics with a potential glycosidase activity.[9]

2. Results and discussion

2.1. One-pot tandem 1,4-addition/aldol reaction

Our synthesis of highly functionalized polyhydroxylated derivatives was initiated from cyclohexenone **1**, easily prepared from methyl α-D-glucoside.[10,11] In the first step we planned to perform the 1,4-addition of a nucleophile at the C3 position, followed by an aldol reaction at the C2 position, which should establish the *trans* relationship between the C2–C3 and C3–C4 substituents (route *a* in Scheme 2). Although an approach involving a 1,4-addition of a nucleophile to cyclic α,β-unsaturated ketones and consecutive trapping such in situ formed enolate by an electrophile (usually an aldehyde) is well-known,[12] the stereochemical output of this transformation seems to be strongly substrate dependent and each case should be considered separately.

Recently, we successfully applied this methodology for the preparation of highly oxygenated decalins with the *trans*-ring junction from *ent*-**1** (Scheme 2).[13]

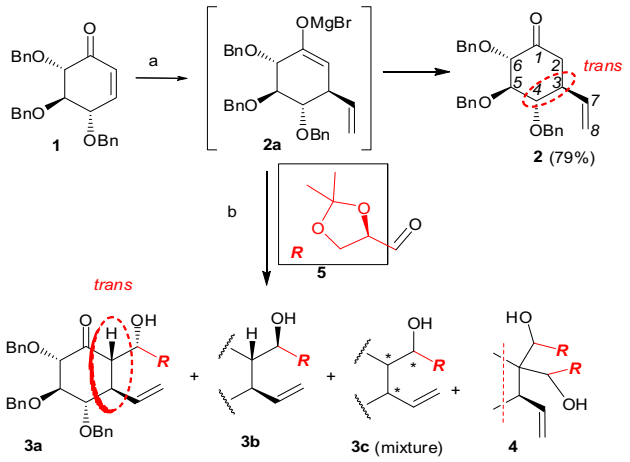


Scheme 2. Plan of the synthesis of the precursors (route a).

Enone **1** was subjected to a one-pot tandem reaction consisting in a 1,4-Michael addition of vinylmagnesium bromide followed by aldol reaction with 2,3-*O*-isopropylidene-D-glyceraldehyde **5** (Scheme 3).

In the initial stage, we examined the stereochemistry of the first step of this tandem reaction i.e., the addition of vinylmagnesium bromide to enone **1** in the presence of CuBr·Me_2S. Derivative **2**, with the expected *trans*-relationship between the C3–C4 substituents (cf. Scheme 2), was obtained as a single stereoisomer in good yield (79%; Scheme 3).

We next turned our attention to the optimization of the reaction conditions of the one-pot transformation leading to **3**. The 1,4-addition of vinylmagnesium bromide to a THF solution of



Scheme 3. Reagents and conditions: (a) CH_2=CHMgBr, CuBr·Me2S, THF, −78 °C, 15 min; (b) see: Table 1.

enone **1** followed by the reaction with 2,3-di-*O*-isopropylidene-D-glyceraldehyde[14] **5** at −78 °C provided **3** in very low yield. We noticed as well that a large excess of aldehyde **5** was needed to obtain products **3** in good yield. However, great care should be taken, since another product, presumably **4**, resulting from the double-aldol reaction, was formed (entry 3; Table 1). This compound was unstable and underwent significant decomposition on silica gel. Since it was also a mixture of diastereoisomers, its structure could not be assigned precisely, and was confirmed only by mass spectrum. The best results were observed when the process was carried out between −78 °C and 0 °C (Table 1; entry 2).

The configurations of products: **2**, **3a**, and **3b** were determined by NMR; see Section 2.3. The stereochemical outcome of this tandem reaction was consistent with the results obtained in our recent approach towards highly oxygenated decalins with the *trans*-ring junction initiated from the enantiomer of enone **1** (Scheme 2).[13]

2.2. Lewis acid-induced domino cyclization/reduction reaction

The next synthetic steps leading to our targets involved an intramolecular migration of the isopropylidene group induced with BF_3·Et_2O. The migration of the isopropylidene block should liberate the primary hydroxyl group followed by closing of the ring to form a hemiacetal. Indeed, when this sequence of reactions was applied to **3a**, it provided the desired compound **6** in 73% yield as the only isomer (Scheme 4). Structure **6** (*trans* ring junction) could be assigned to this product on the basis of the NMR data (see Section 2.3). The reduction of **6** with triethylsilane–BF_3·Et_2O afforded highly stereoselectively tetrahydropyran **7** in 82% yield (61% from **3a**) to which also the *trans*-configuration at the rings junction was also assigned (see Fig. 1 in Section 2.3).

Finally, we performed this transformation through a one-pot fashion and obtained **7** in the same reasonable yield (61%). Our

Table 1
Optimization of the second step of one-pot three-component transformation leading to **3**

Entry	**5** (equiv)	Temperature	Yield[a]	**3a**:**3b**:**3c**[b]	Yield[a] **2** (%)	Yield[c] **4** (%)
1	4.2	−78 °C	32	84:9:7	29	–
2	**4.2**	**−78 °C → 0 °C**	**71**	**88:8:4**	–	**14**
3	9.6	−78 °C → 0 °C[b]	47	Not defined	–	39

[a] Isolated yield.
[b] Determined by HPLC on crude mixture (**3c** was an inseparable mixture of stereoisomers different than **3a** and **3b**).
[c] Mixture of stereoisomers of a double-aldol reaction (by MS) after chromatography, but partly degraded.