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Magnesium(II)-coordinated Claisen rearrangement: a direct approach towards ulosonic acid derivatives

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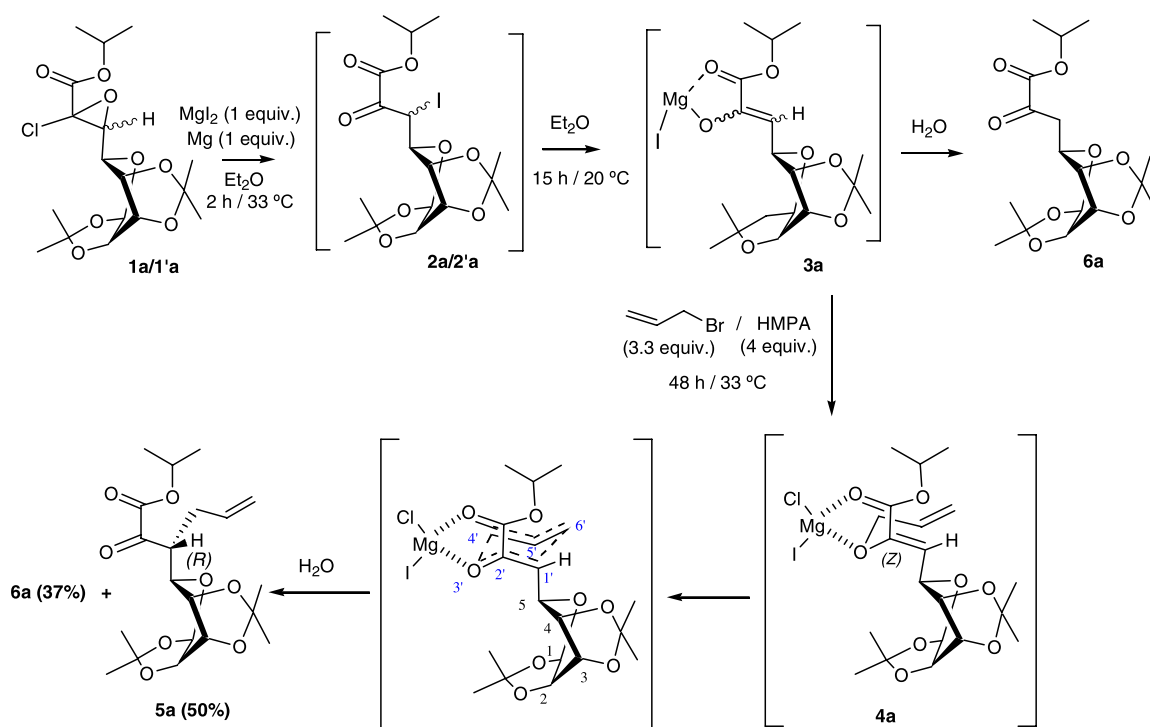
The Claisen rearrangement is one of the most valuable synthetic methods for C–C bond stereocontrolled formation.¹ The utility of this 3,3-sigmatropic rearrangement and its variants rests on their ability to change the molecular framework significantly within a single step and with an interesting transfer of chirality.² Unfortunately, the possibility of wide applications of the Claisen rearrangement in carbohydrate chemistry is strongly reduced by rather hard reaction conditions and by the restricted availability of the starting enol ethers. The most frequent use of the carbohydrate-based Claisen rearrangement concerns glycals and other endocyclic unsaturated derivatives.³ In another connection, the Lewis acid ability of increasing both reaction rate and selectivity of pericyclic reactions as cycloadditions is well known.⁴ Recent results of chiral metal complexes directed Claisen rearrangements have been described,⁵ particularly ester and amide enolate Claisen rearrangements.⁶ Important and recent contributions of Hierse-mann et al., develop catalytic enantioselective Claisen rearrangement of 2-alkoxycarbonyl- and 2-(1,3-oxazolin-2-yl)-substituted allyl vinyl ethers.⁷ The efficiency of the copper BOX (bis-oxazoline) catalysts complements

the promising preliminary results of the Pd(II) systems.^{4,8} However, the application of the catalysed Claisen rearrangement in carbohydrate chemistry seems undescribed. Consequently, a catalytic asymmetric Claisen rearrangement represents an attractive challenge to design synthesis of new complex glucidic structures as mimic sugars and highly functionalised chiral carbocycles.

In this letter, we present the study of a one-pot stereo-selective Claisen rearrangement of allyl ether of enols such as **4a**, into **5a**, catalysed by magnesium dihalide, with a first synthetic application to the stereoselective construction of a disaccharide analogue **8a/8'a** including a galactosyl and an ulosonic isopropyl ester moieties. Recently, we described the first preparation of magnesium α -ketoester enolates **3** from easily available α -chloroglycidic esters **1** and magnesium diiodide in the presence of an excess of active magnesium. Due to their high stability, these magnesium enolates react with strong alkylating reagents such as chloromethylmethyl ether and dimethylsulfate in the presence of an excess of HMPA to afford only the O-alkylation products.⁹ On the basis of these previous works, the reaction of the magnesium enolate **3a** derived from the diastereomeric mixture of isopropyl α -chloroglycidic ester **1a/1'a** and allyl bromide was examined with a view to prepare the starting allyl ether of α -ketoester enol **4a** (Scheme 1). As we assumed, the reaction was rather slow, due to

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Scheme 1.

the poor reactivity of enolate **3a**. Surprisingly, the *C*-allyl product **5a** was the major product accompanied by a small amount of the expected *O*-allyl product **4a**. This result was not in accord with our earlier studies since such magnesium enolates gave only *O*-alkylation, *O*-silylation and *O*-phosphorylation.^{9a} Consequently, a slow *O*-allylation followed by a Claisen rearrangement leading to the *C*-allylation product was supposed. The Claisen rearrangement occurred in the reaction medium as the slow *O*-allylation proceeded, leading finally after 48 h at 33 °C to the desired product **5a** in 50% yield accompanied by α -ketoester **6a** and a trace of **4a**. The latter compound **6a** resulted from the hydrolysis of the unreacted starting magnesium enolate **3a** and was easily separated from **5a** (37% yield after a chromatographic purification).

The 100% stereoselectivity of the process that provides **5a** as a unique diastereomer has to be noted. The configuration of the new chiral carbon C-6 formed in the rearrangement can be deduced from the well-known chair transition state model for the allyl vinyl ether if the configuration of the trisubstituted carbon-carbon double bond of **4a** is known. The chemical shift of H-6 at 6.25 ppm in **4a** is characteristic for the (*Z*) *O*-alkyl enols in the galactose series.^{9a} Therefore, we imagine a possible transition state in which the allyl unit is on the opposite side to the isopropylidene ketal at C3-C4 and in front of the *Si* face of the trisubstituted carbon-carbon double bond. Such a transition state has to lead to the sole (*R*)-configuration for C-6 in **5a**.

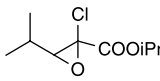
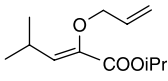
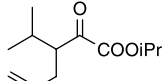
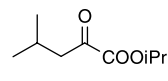
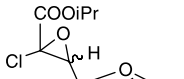
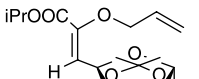
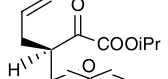
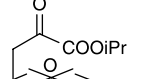
Definitive evidence for such an assignment was provided by the determination of the crystal structure of **5a** that confirmed the (*R*)-configuration.¹⁰ The asymmetric

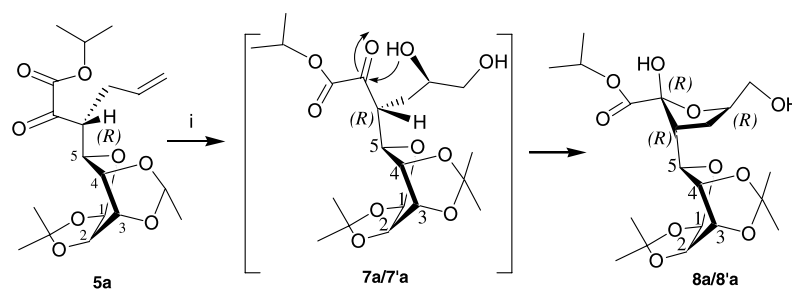
inducting effect of the chiral pyranic ring placed outside of the six centres of the chair transition state has to be noted.¹¹ In the present case, magnesium dihalide seems to play a crucial role in terms of stereocontrol as an efficient tool to fix a defined and single transition state conformation and to maximise asymmetric induction. It allows also to carry out the rearrangement under mild reaction conditions at low temperature.

This one-pot magnesium-catalysed Claisen rearrangement was extended to two other substrates (Table 1). In the experimental conditions described in Scheme 1, α -chloroglycidic esters **1b** and **1c** led to a mixture of *O*- and *C*-allyl derivatives **4** and **5** in which the product of *C*-allylation **5** was the major product. Whereas pure **5c** could be obtained by chromatographic purification from the mixture **4c/5c** (30% yield from **1c**), the separation of **4b** from **5b** by chromatography did not succeed. This difficulty brought us to find the optimum conditions for the reaction to proceed to completion. When the mixture **4b/5b** was heated at 33 °C for an extended time (12 h) in the presence of MgI₂, the *C*-allyl product **5b** was exclusively obtained (53% yield in pure product from **1b**). The reaction was repeated in the absence of MgI₂, in xylene at reflux to promote the possible thermal rearrangement. Only degradation of substrates was observed. These results supported our conclusion that MgI₂ catalysed the process and showed the great utility of this catalysis in Claisen rearrangement applied to thermally sensitive carbohydrates.

In connection with our interest in the synthesis of bioactive ulosonic acids and analogues, the strategy was used to provide key intermediates for the preparation of biologically active ulosonic acids. These glucidic

Table 1.

Starting material	4	5	6
 1b	 4b (19%)	 5b (42%)	 6b (39%)
 1c	 4c (17%)	 5c (46%)	 6c (37%)

**Scheme 2.** Reagents and conditions: (i) OsO₄/NMO, 24 h (95% yield, de: 3/2) or AD-mix-β, 48 h (90% yield, de: 9/1).

α -ketoacids are involved in biosynthetic pathways of bacteria and constitute important targets for the design of new antibacterial agents.¹² The *C*-allyl ketoester **5a** represented a key precursor for the synthesis of the disaccharide analogue **8** in which an ulosonic residue could be installed via the dihydroxylation of the double bond of **5a** (Scheme 2). The asymmetric dihydroxylation of **5a** was investigated using either the achiral reagent osmium tetroxide-*N*-methyl-morpholine *N*-oxide (NMO/OsO₄) or osmium tetroxide in the presence of quinidine ligand (AD-mix-β) under conditions of the Sharpless asymmetric dihydroxylation (SAD).¹³

Compound **5a** efficiently reacted with the two systems, NMO/OsO₄ and AD-mix-β. However, the reaction was more rapid with the classical achiral reagent NMO/OsO₄ as the result of a low steric hindrance of the corresponding transition state compared with that including quinidine ligand of AD-mix-β. The formed diol intermediate **7a/7'a** led to a cyclisation in situ to give the ulosonic ester **8a/8'a**. Although the reaction led to the formation of two new asymmetric centres, only two stereoisomers were observed in ¹H and ¹³C NMR. In contrast with NMO/OsO₄ that gave a diastereomeric ratio of 3/2 for **8a/8'a**, a better stereoselectivity was obtained with AD-mix-β (9/1) and could be compared favourably with recent reports in the literature relating the asymmetric dihydroxylation of exocyclic double bond of glucidic allyl ether.¹⁴ Taking into account these different stereoselectivities and the mechanism of the dihydroxylation reaction, we suppose that both epimers **8a** and **8'a** are the result of a partial stereochemical induction during the asymmetric dihydroxylation with a same α or β configuration for the anomeric carbon of the ulosonic moiety. The major iso-

mer of the initial 9/1 mixture **8a/8'a** was obtained in pure state after chromatography and its structure was completely determined by a fine NMR study (see Supplementary data).¹⁵

In conclusion, we successfully describe a rapid synthesis of aliphatic and glucidic *C*-allyl α -ketoesters based on magnesium dihalide-catalysed Claisen rearrangement. Starting materials are easily accessible from simple precursor α -chloroglycidic esters. The process is unprecedented in glucidic series and proceeds with a total stereoselectivity, leading to highly functionalised carbohydrates. A first application of this strategy allows the access to a new disaccharide analogue including an ulosonic unit. The structure of this new compound has been completely determined by a fine NMR study. Further studies are under investigation to extend the synthetic potential of this process to other carbohydrates.

Supplementary data

Experimental procedures, analytical data and copies of NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.07.022](https://doi.org/10.1016/j.tetlet.2006.07.022).

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- 6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(2-propenyl)-*L*-glycero- α -D-galacto-7-octulose-1,5-pyranuronic acid isopropyl ester **5a**: White solid. R_f (EtOAc/hexane 1:4) = 0.4; mp 57 °C; $[\alpha]_D^{23}$ 1.23 (*c* 1.2, CH₂Cl₂); IR (film): ν 1726, 1639 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.65 (H₁₂, 1H, m), 5.47 (H₁, 1H, d, *J* = 5.1 Hz), 5.07 (H₉, 1H, hpt, *J* = 6.3), 5.00–4.92 (H₁₃, 2H, m), 4.49 (H₃, 1H, dd, *J* = 2.5, 7.8 Hz), 4.25 (H₂, 1H, dd, *J* = 5.1, 2.5 Hz), 4.08 (H₄, 1H, dd, *J* = 2.5, 7.8 Hz), 3.89 (H₅, 1H, dd, *J* = 2.0, 9.5 Hz), 3.74 (H₆, 1H, m), 2.5 (H₁₁, 1H, m), 1.46 (CH₃, 3H, s), 1.36 (CH₃, 3H, s), 1.27 (H₁₀, 6H, d, *J* = 6.3 Hz), 1.25 (CH₃, 3H, s), 1.19 (CH₃, 3H, s); ¹³C NMR (100 MHz, CDCl₃): δ 195.9 (C₇, 1C), 160.4 (C₈, 1C), 133.5 (C₁₂, 1C), 118.2 (C₁₃, 1C), 109.3 and 108.8 (C(CH₃)₂, 2C), 96.5 (C₁, 1C), 70.9 (C₄, 1C), 70.8 (C₃, 1C), 70.5 and 70.3 (C₂ and C₉, 2C), 67.1 (C₅, 1C), 47.4 (C₆, 1C), 32.8 (C₁₁, 1C), 25.96 (CH₃, 1C), 25.91 (CH₃, 1C), 25.0 (CH₃, 1C), 24.6 (CH₃, 1C), 21.6 (C₁₀, 2C); SM (ESI > 0.40 V): 421.2 [M+Na]⁺. Anal. Calcd for C₂₀H₃₀O₈: C, 60.29; H, 7.59; O, 32.12. Found: C, 60.52; H, 7.46.
Major diastereomer **8a**: IR (film) ν 3680–3060, 1731 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆): δ 5.60 (OH_{2'}, 1H, d, *J* = 1.3 Hz), 5.44 (H₁, 1H, d, *J* = 5.0 Hz), 4.95 (H_{7'}, 1H, heptuplet, *J* = 6.3 Hz), 4.55 (H₃, 1H, dd, *J* = 2.4, 8.0 Hz), 4.40–4.33 (H_{5'}, 1H, m), 4.30 (H₂, 1H, dd, *J* = 2.4, 5.0 Hz), 4.21 (H₄, 1H, dd, *J* = 1.7, 8.0 Hz), 3.87 (H₅, 1H, dd, *J* = 1.7, 10.0 Hz), 3.58–3.47 (H_{6'a}, H_{6'b}, 2H, m), 3.42 (OH_{6'}, 1H, dd, *J* = 5.3, 7.3 Hz), 3.00–2.95 (H_{3'}, 1H, m), 2.20–2.05 (H_{4'a}H_{4'b}, 2H, m), 1.49 (H_{7b}, 3H, s), 1.36 (H_{9b}, 3H, s), 1.31 (H_{7a}, 3H, s), 1.30 (H_{8'b}, 3H, s), 1.27 (H_{8'a}, 3H, s), 1.26 (H_{9a}, 3H, s); ¹³C NMR (100 MHz, acetone-*d*₆): δ 170.80 (C_{1'}, 1C), 108.44 (C₈, 1C), 108.03 (C₆, 1C), 101.40 (C_{2'}, 1C), 96.38 (C₁, 1C), 79.98 (C_{5'}, 1C), 70.87 (C₄, 1C), 70.63 (C₃, 1C), 70.39 (C₂, 1C), 69.48 (C₇, 1C), 68.39 (C₅, 1C), 64.55 (C_{6'}, 1C), 45.51 (C_{3'}, 1C), 32.21 (C_{4'}, 1C), 25.53 (C_{9b}, 1C), 25.40 (C_{7b}, 1C), 24.31 (C_{7a}, 1C), 23.65 (C_{9a}, 1C), 20.96 (C_{8'b}, 1C), 20.93 (C_{8'a}, 1C); SM (ESI > 0, 40 V): 455.07 [M+Na]⁺. Anal. Calcd for C₂₀H₃₂O₁₀: C, 55.55; H, 7.46; O, 37.00. Found: C, 55.32; H, 7.67.