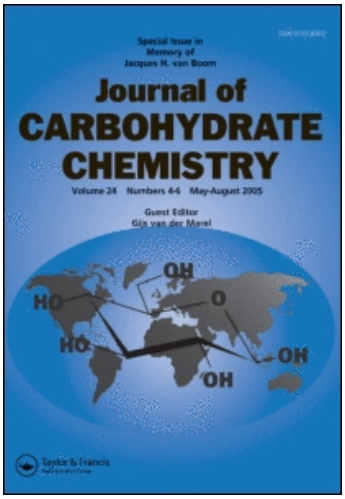

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Jürs, Stefan and Thiem, Joachim(2005) 'Conversion of an Arabinose-Derived Allyl Vinyl Ether System into the Functionalized 4-Cycloheptenone via Claisen Rearrangement', Journal of Carbohydrate Chemistry, 24: 8, 843 — 847
To link to this Article: DOI: 10.1080/07328300500434224
URL: http://dx.doi.org/10.1080/07328300500434224

Journal of Carbohydrate Chemistry, 24:843–847, 2005

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300500434224

Conversion of an Arabinose-Derived Allyl Vinyl Ether System into the Functionalized 4-Cycloheptenone via Claisen Rearrangement

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Keywords Claisen rearrangement, Carbocycles, Allyl vinyl ethers

A large number of natural products display seven-membered rings as a distinctive structural feature.[1] Since they frequently contain both oxygenated functions and stereogenic centers, their synthesis is quite demanding, particularly starting from achiral compounds. The employment of carbohydrate derivatives proved to be a useful alternative for a number of synthetic purposes in natural product chemistry.[2] Previous reports have shown the successful application of the Claisen rearrangement on pyranoses for ring enlargement purposes to give eight-membered ring structures.[3–5] In contrast to these findings, furanoses have attained relatively little attention with regard to corresponding synthetic approaches. Recently, Zhang et al. reported on the synthesis of a seven-

Dedicated to the memory of Prof. Jacques van Boom.

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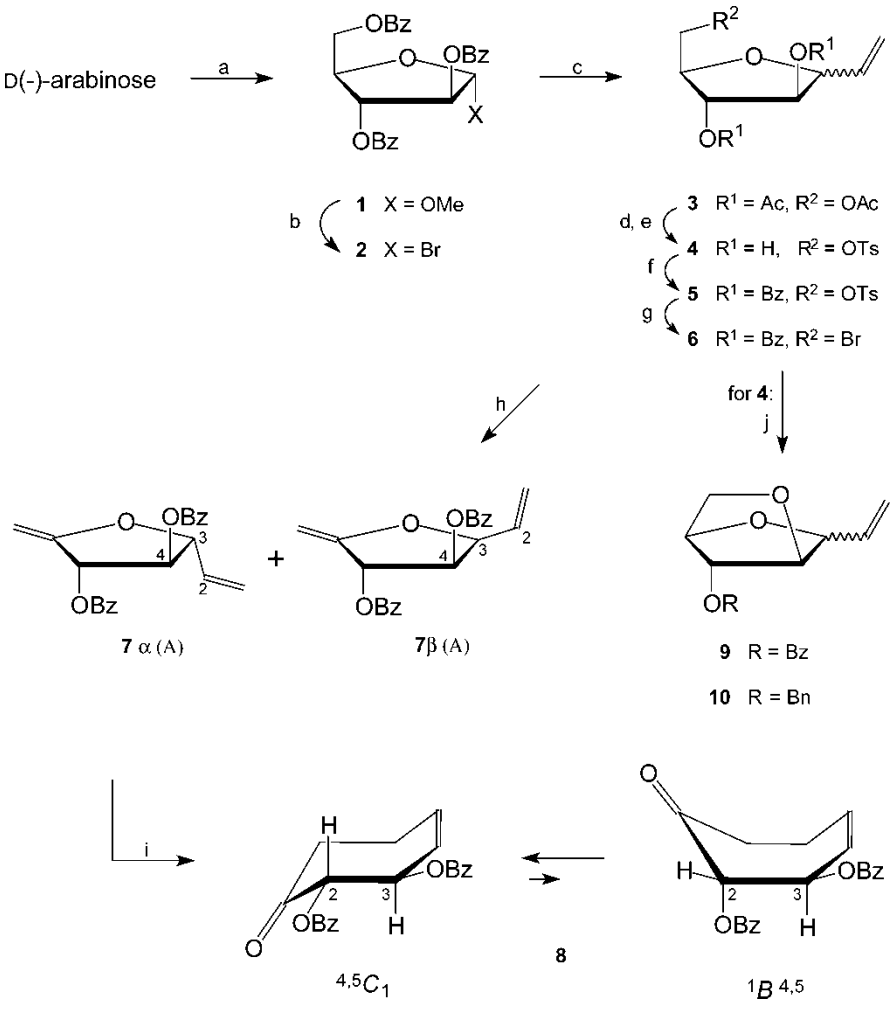
membered carbocycle starting from D-glucose. The whole reaction sequence involved 11 steps, which seems to be a rather extended route for a relatively simple but useful chiral building block.[6] Krohn et al. observed the formation of a seven-membered carbocycle by intramolecular carbocyclization of an open-chain sugar derivative in a 14-step sequence.[7] The present communication outlines a considerably shorter approach toward a chiral cycloheptenone derivative involving Claisen rearrangement of a properly functionalized furanose.

Considering the progress in *C*-glycoside synthesis in recent years, the introduction of a vinyl group at the anomeric center of a furanose was considered to be feasible using an α-halide. To make use of the Claisen rearrangement in the sense of a ring enlargement, the generation of a second double bond would be required to furnish the allyl vinyl ether substructure. Thus, D-(−)-arabinose was chosen as starting material and the highly reactive α-furanosylbromide **2** synthesized according to Fletcher's procedure[8] (Sch. 1).

The subsequent Grignard reaction using vinylmagnesiumbromide[9] gave **3** in 66% yield. It should be emphasized that this is unexpectedly successful because yields in this type of *C*-glycosylations with peracylated carbohydrates are usually between 25% and 45% due to competing elimination reactions. Apparently, in this case, the elimination is much less favored due to the *cis* orientation of both the 2-benzoate and the α-bromide in relation to the hydrogen atom on the adjacent carbon. The obtained anomeric mixture was peracetylated to facilitate the separation from large amounts of inorganic salts. After deacetylation under Zemplén conditions,[10] the primary OH-group could be selectively tosylated to give **4** and directly transformed by benzoylation to give **5**. The tosylation was accompanied by the formation of the bicyclic anhydro side product **9** in moderate amounts. For the same reason the introduction of benzyl groups (NaH, BnBr, DMF) was not successful since **10** was formed in major amounts under these stronger basic conditions.

The tosylate **5** was transformed into the bromide **6** by Finkelstein reaction. By subsequent elimination using silver fluoride in pyridine,[11] the synthesis of the exocyclic enol ether **7** was accomplished and the product obtained as an inseparable mixture of anomers. In contrast to previous reports of corresponding yet unsubstituted 2-vinyl-5-methylene-tetrahydrofuranes,[12] compounds **7α** and **7β** proved to be surprisingly stable even during column chromatography and could be stored for an extended time at −18°C without decomposition. No isomerization to the internal enol ether with dihydrofurane structure (furanoide glycal) could be observed.

In an initial attempt to effect rearrangement, the mixture of compounds **7α** and **7β** was heated to 100°C in DMSO with bis[1,2-bis(diphenylphosphino)ethane]palladium as catalyst. Whereas Trost et al.[13] were able to rearrange several furanose derivatives to the corresponding cycloheptenones using this methodology, it did not effect any conversion in this case. Hence,



Scheme 1: Claisen rearrangement of a D-(−)-arabinose derived furanose precursor a) AcCl, MeOH, then BzCl, py, 79%; b) HBr/HOAc, in situ; c) CH_2=CHMgBr, THF, then Ac_2O, py; 66%; d) NaOMe, MeOH, 100%; e) TsCl, py; f) BzCl, DMAP, py, 61% (two steps); g) NaBr, DMF, 70° C, 100%; h) AgF, py, 52%; i) decane/toluene 6:1, microwave, 180° C, 20 min, 54%; j) "basic conditions" (TsCl, py; NaH, BnBr, DMF, respectively).

the thermal method was employed using nonoxygenated solvents to avoid decomposition and formation of side products. Furthermore, a preferably high heat capacity of the solvent should effect an improved energy transfer onto the substrate. These considerations prompted the use of decane as solvent with an addition of toluene to improve solubility.[a] Under

[a]Concentration of **7** in decane/toluene 6:1 approx. 0.013 M.

these conditions, the enantiopure product **8**[b] could be isolated in 54% yield together with 46% of a recovered **7α** and **7β** mixture. Its ^{1}H NMR spectrum confirmed the presence of an anomeric mixture, however, with the opposite α/β-ratio (A:B $\approx$ 1:2) compared to the precursor **7α** and **7β** mixture (A:B $\approx$ 2:1). This suggests that one anomer A undergoes the Claisen rearrangement exclusively or at least much faster than the other anomer B. To verify this assumption, the amount of recovered **7α** and **7β** mixture was heated again under the same conditions as before, which resulted in the complete consumption of A. Since the exact determination of the anomeric configuration by means of coupling constants is usually unreliable for furanoses, NOE spectra were recorded. In spite of the minor signal intensity (H-2_A:H-2_B = 0.5:1.0), a stronger NOE between H-2_A and H-4_A than between H-2_B and H-4_B was observed, indicating a greater spacial proximity of the former. Hence, the faster rearranging anomer A presumably corresponds to the α-anomer.

The 4-cycloheptenone derivative **8** contains a (*Z*)-configurated double bond, which is energetically favorable during the Claisen process since it is positioned within a ring. For the 4-cycloheptenone system itself, there are only the two conformations boat—(*B*) and chair (*C*).[14] Generally, the chair conformation is preferred due to minimized van der Waals repulsions of the π-electrons. Since the NMR spectra of **8** showed sharp signals of only one single conformer in benzene solution, this compound is assumed to feature the chair conformation ($^{4,5}C_1$) with a *trans*-diaxial arrangement of H-2 and H-3, supported by a large vicinal coupling constant ($J_{2,3}$ = 9.7 Hz). The exact determination of the actual conformation of **8** in the solid state depends on X-ray analysis, and current attempts are being made to obtain suitable crystals of compound **8** or other derivatives.

ACKNOWLEDGEMENT

The support of this work by the Deutsche Forschungsgemeinschaft (GRK 464) and the Fonds der Chemischen Industrie is gratefully acknowledged.

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[b]Compound **8**: mp: 102–104°C; $[\alpha]_{546}^{20}$ -84 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, C_6D_6): (= 1.45–1.54 (m, 1 H, H-6b), 1.95–2.05 (m, 1 H, H-6a), 2.14–2.22 (m, 1 H, H-7b), 2.27 (ddd, 1 H, H-7a), 5.41–5.48 (m, 1 H, H-5), 5.56 (ddd, 1 H, H-4, $J_{3,4}$ = 3.8, $J_{4,5}$ = 11.8 Hz), 6.11 (d, 1 H, H-2, $J_{2,3}$ = 9.7 Hz), 6.23–6.27 (m, 1 H, H-3, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.8 Hz), 6.85–7.11, 8.10–8.17 (2 × m, 10 H, Ar) ppm. ^{13}C NMR (100 MHz, C_6D_6): (= 22.1 (1 C, C-6), 40.4 (1 C, C-7), 70.2 (1 C, C-3), 78.9 (1 C, C-2), 127.7–128.6, 130.0, 130.2, 132.7, 133.3 (14 C, C-4, C-5, Ar), 165.7, 165.9 (2 C, $PhCO_2$), 201.1 (1 C, CO) ppm. Anal. Calcd for $C_{21}H_{18}O_5$ (350.39): MALDI-TOF: *m/z* 373.2 (M + Na), 389.1 (M + K).

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