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Claisen–Ireland rearrangement: a new route to *C*-glycosides

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Abstract

A Claisen–Ireland rearrangement led to the formation of *C*-glycan derivatives. Azidonitration–reduction or dihydroxylation afforded gluco- and galacto-derived β-*C*-glycosides. Subsequent deprotonation of bicyclic lactones **16** allowed the control of the newly created asymmetric centre. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Serine or threonine *O*-glycoconjugates are constituents of various glycopeptides which play a key role in inflammation, in adhesion of viruses and bacteria to cells and in cell to cell communication.[1] The synthesis of related *C*-glycopeptides in which the natural *O*-glycosyl linkage is replaced by a non-hydrolysable C–C bond is the subject of intensive research.[2] A new strategy using a Claisen–Ireland [3,3] sigmatropic rearrangement leading to analogous C1 functionalised *C*-glycosides (β-configuration), as well as further transformations of the resulting glycal derivatives, are presented herein.

Few examples of [3,3] sigmatropic rearrangement mediated syntheses of *C*-glycosides have already been described in the literature.[3] Glycal derivatives are used as starting material in these reactions. We anticipated that 1-*exo*-methylene saccharides **1** bearing on position 3 various ester groups could lead to rearranged glycal derivatives **3**, after deprotonation–silylation and rearrangement according to the Claisen–Ireland methodology. Azidonitration of the resulting enol ether double bond in **3**, followed by the reduction of both azido group and anomeric position, should give rise to various *C*-glucosamine or galactosamine derivatives **4** (Scheme 1). The major advantage of this methodology results from the versatility of the nature of the ester group which can be introduced on C3 alcohol. However, two questions are addressed from this anticipated scheme. The first one concerns the reactivity of this system in which oxygen atoms in the 1,5-dienic unit are in 'mismatch' position from an electronic point of view. The second point is related to the diastereoselectivity of this rearrangement which depends on the geometrical control during enolate formation and on the conformation in the transition state.

Claisen–Ireland rearrangement has been studied on both galactose and glucose derivatives. In galactose series, compound **7** was prepared following a known sequence of reactions. Accordingly, tribenzyl

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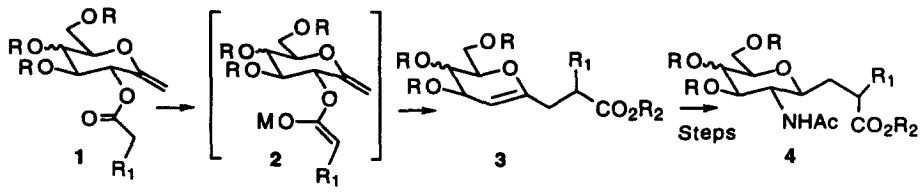
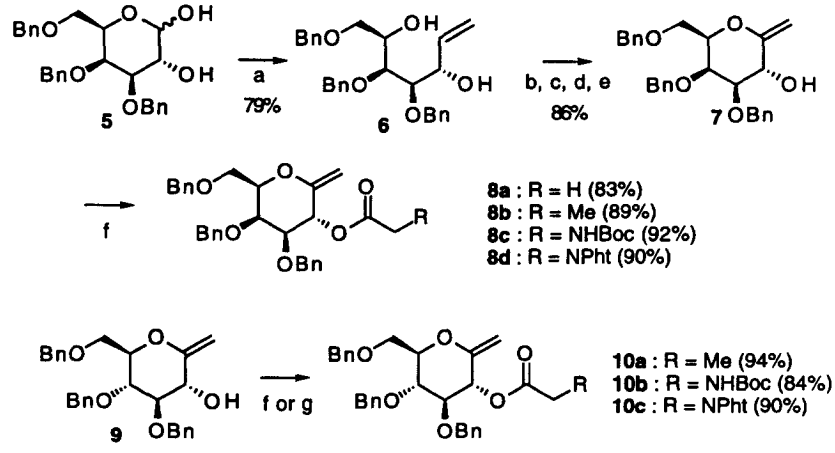


Scheme 1.

derivative **5**[4] submitted to a Wittig olefination[5] afforded compound **6** (Scheme 2). A four-step sequence following the methodology described by Nicotra,[6] gave rise to the expected pivotal *exo*-methylene galactose derivative **7** in 86% overall yield. Classical esterification afforded the esters **8a–8d**. In the glucose series, compound **9** was prepared in 64% overall yield for five steps from 2,3,5-tri-*O*-benzyl-D-arabinofuranose following a previously described methodology.[6b,7] Subsequent esterification of **9** with propionyl or glycine units afforded the esters **10a–10c**.



Scheme 2. (a) $Ph_3P^+MeBr^-$, *n*-BuLi, THF. (b) $Hg(OAc)_2$, THF. (c) KCl, THF, H_2O. (d) I_2, CH_2Cl_2. (e) DBU, PhMe. (f) RCOCl, C_5H_5N, DMAP, CH_2Cl_2, (**8a**, **8b**, **10a**). (g) RCO_2H, DCC, DMAP, CH_2Cl_2, (**8c**, **10b**) or AcOEt, MeCN (**8d**, **10c**)

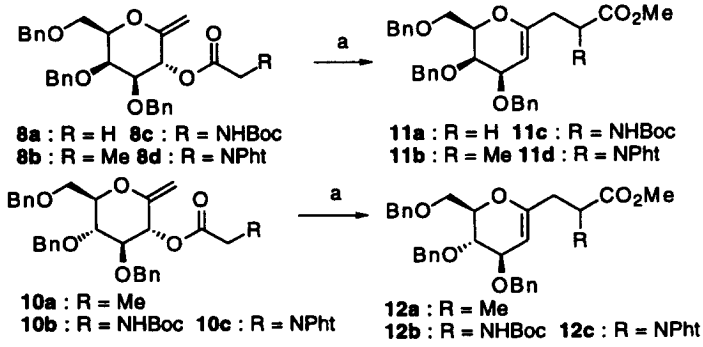
With ester derivatives **8a–8d** and **10a–10c** in hand, the crucial Claisen–Ireland rearrangement[8] in which the heteroatoms are in 'mismatch' position on the 1,5-dienic unit was then examined. Ester **8b** was first chosen as a model. The results are summarised in Table 1. Deprotonation, silylation, rearrangement and diazomethane esterification were performed without isolation of the intermediates.[9]

Table 1

entry	starting material	base / solvent	time (h)	product	yield%	d.s.
1	**8b**	LDA / THF	15	**8b**	85	
2	**8b**	KHMDS / THF	15	**11b + 8b**	30 +60	
3	**8b**	KHMDS / toluene (a)	15	**11b + 8b**	91 + 6	64 : 36
4	**8a**	KHMDS / toluene (a)	15	**11a**	13	
5	**8c**	KHMDS / toluene (b)	3	**11c**	38	52 : 48
6	**8d**	KHMDS / toluene (a)	3	**11d**	32	52 : 48
7	**10a**	KHMDS / toluene (a)	15	**12a**	81	58 : 42
8	**10b**	KHMDS / toluene (b)	3	**12b**	72	95 : 5
9	**10c**	KHMDS / toluene (a)	3	**12c**	93	68 : 32

(a) KHMDS, TMSCl, 2 equiv. (b) KHMDS, TMSCl, 4 equiv.

Comparison between entries 1–3 showed that both the nature of the metal and solvent are crucial in this reaction (Table 1 and Scheme 3). With lithium diisopropylamide, the starting material is recovered without any transposition. The lack of reactivity in this case could be due to a strong chelation of the lithium cation by the ether functional groups which could preclude the deprotonation of the ester.[10] With potassium cation, this chelating effect is probably decreased. Best results were obtained when potassium bis(trimethylsilyl)amide in solution in toluene is used (entry 3). In this case, for a starting concentration of 0.1 M in tetrahydrofurane, the reaction medium contained a mixture of toluene:THF in 30:70 ratio. However, the influence of this less polar solvent is difficult to rationalise. With the exception of the acetyl ester (entry 4), yields are moderate to good, better results being generally obtained in the glucose series (entries 7–9).



Scheme 3. (a) See Table 1 and typical transposition[9]

The diastereoselectivity of these reactions were estimated either by ^1H NMR in toluene-d_8 for the side chain methyl and/or by ^{13}C NMR, the chemical shift of the C3 in glycal derivatives being different for each diastereomer. In addition, *exo*-methylene deuterated **8b** was prepared by a Wittig reaction with $Ph_3P^+CD_3I^-$. The diastereoselectivity determined by Courtieu's method[11] applied to the resulting ester **11b**, deuterated on the methylene side chain, is in accord with the value measured by ^{13}C NMR. The absolute configuration of the centre on the side chain was determined after chemical transformations (vide infra).

Accordingly, compound **11b** was treated by ceric ammonium nitrate–sodium azide[12] and afforded an azido-nitrate intermediate which was submitted without any purification to a reduction at the anomeric carbon. β-*C*-Glycoside **13** was thus isolated. Nickel boride reduction of the azido functional group led to the concomitant formation of the lactam derivative **14**. Similarly, dihydroxylation of compound **11b** afforded smoothly, and in good yield, lactone **15**. Esterification[13] of the tertiary alcohol in **15** with benzoic anhydride and tri-*n*-butylphosphine led to ester derivatives **16a** and **16b** (Scheme 4). Deprotonation of the 35:65 mixture of diastereomeric esters **16a**:**16b** with KHMDS followed by reprotonation afforded **16a**:**16b** in an unoptimised 20:80 ratio. This reequilibration overcomes the poor diastereoselectivity of the Claisen–Ireland rearrangement. Moreover, NOESY experiments secured the configuration of the methyl substituted carbon in **16b** (Fig. 1).

Acknowledgements

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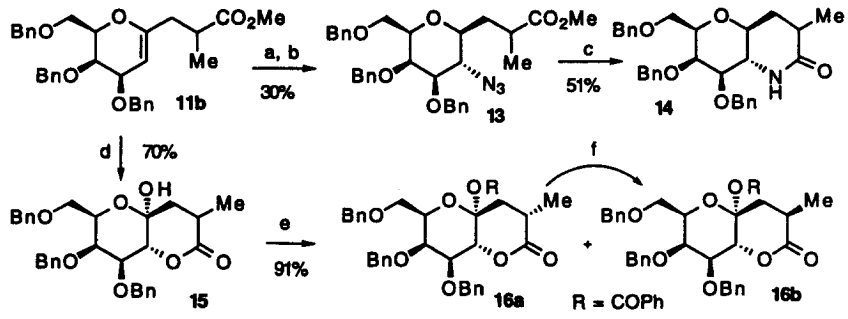

Scheme 4. (a) CAN, NaN_3, MeCN, –20°C. (b) Et_3SiH, BF_3Et_2O, MeCN. (c) $NaBH_4$, $NiCl_2$, 6 H_2O, EtOH, rt. (d) OsO_4, 0.1 equiv., NMO, 3 equiv., $MeSO_2NH_2$, *t*BuOH, H_2O 1:1, rt, 2 h. (e) PBu_3, Bz_2O, CH_2Cl_2, rt, 30 min. (f) KHMDS, THF, –78 to –20°C, 30 min.

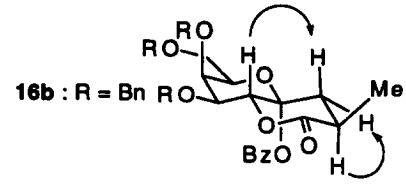

Figure 1.

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