n-Pentenyl Esters Facilitate an Oxidative Alternative to the Ferrier Rearrangement. An Expeditious Route to Sucrose

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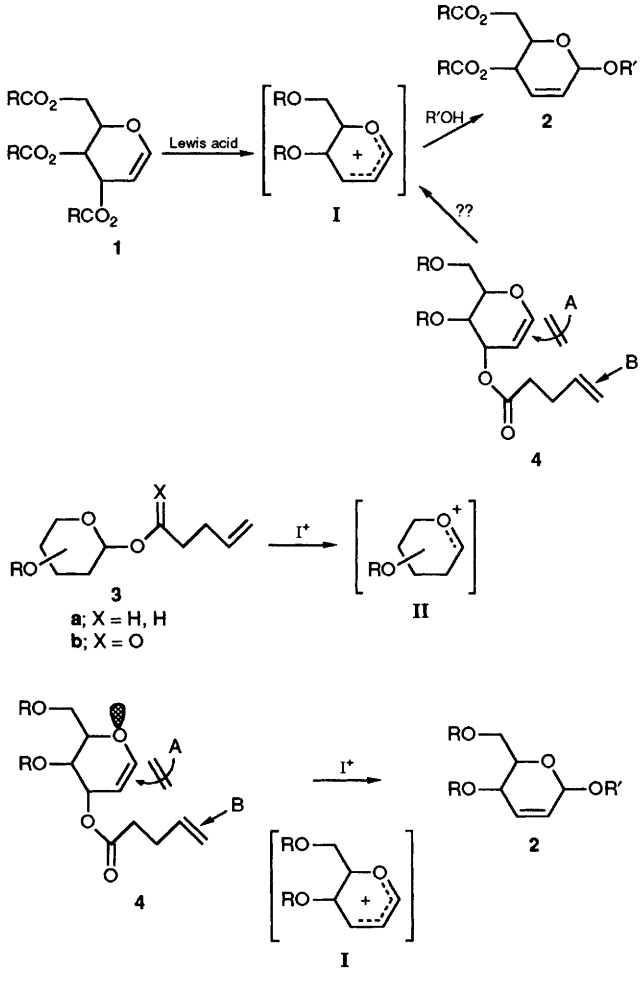
Ferrier-type reactions can now be carried out under non-acidic conditions by treating 3-n-pentenoyl glycals with iodonium dicollidinium perchlorate whereupon the terminal double bond is chemoselectively activated to furnish an allylic oxo-carbenium ion which reacts at the anomeric position with monosaccharide alcohols to afford 2,3-unsaturated disaccharides in fairly good yields.

The Ferrier reaction,[1] **1**→**I**→**2**, is the method of choice for the synthesis of 2,3-unsaturated glycosides[2] **2**. However the requirement of an acid catalyst[3] precludes the use of acid-sensitive protecting groups, and the development of a non-acidic alternative would extend the scope of the reaction. In this manuscript we describe such a procedure which, *inter alia* helps to clarify aspects of the Ferrier reaction.

The present study grew out of our investigation of n-pentenyl esters (NPEs) as glycosyl donors[4], **3b**→**II**. Although these substrates underwent coupling reactions readily, they



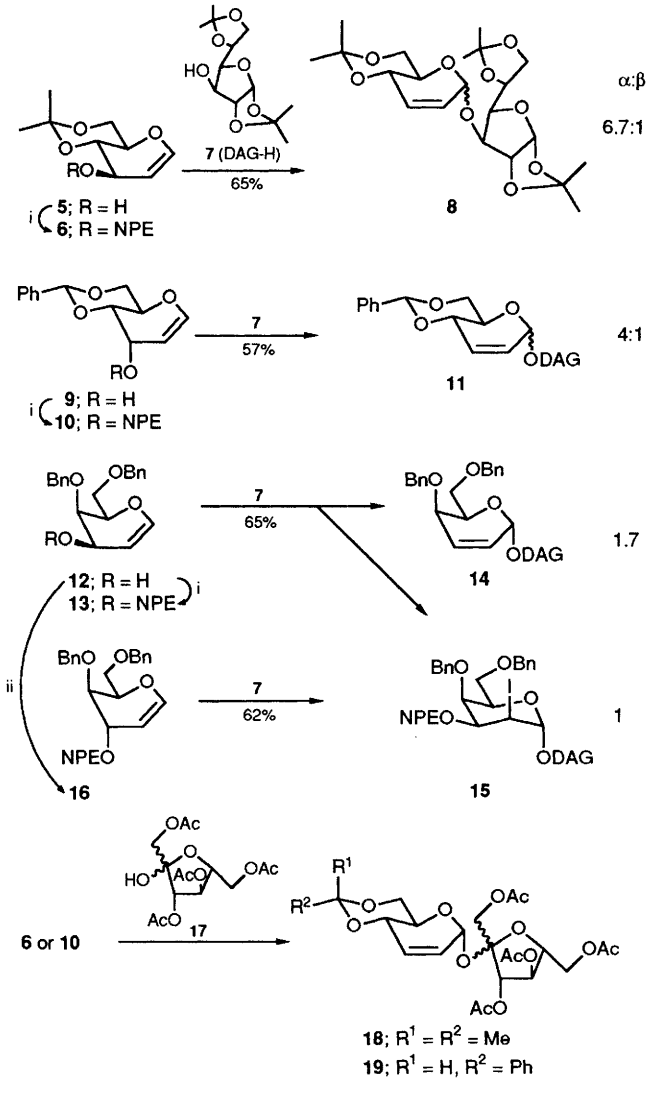
did not display armed–disarmed effects[5] to the extent that had been observed with their n-pentenyl glycoside (NPG) counterparts,[6,7] and, since our original observations,[5] extended to other glycosyl donors.[8–10] However in attempting to develop chemistry that would be unique for these esters, we noted that by placing the group at C-3, the molecule, **4**, would be a vinylogous glycosyl ester, whose oxidative cleavage would yield the allyl oxo-carbenium intermediate **I** of the Ferrier reaction.

Compound **4** has two possible sites for electrophilic attack, and the question of chemoselectivity arose. The vinyl ether of **4**, A, should be more reactive towards an iodonium ion than the isolated pentenyl double bond, B. On the other hand, Friesen and Danishefsky had shown that C-3 esters disarm a glycal double bond.[9a] Whether this delicate counterplay of electronic forces could be resolved was the objective of this study.

Our first test substrate was ester **6** which was readily prepared from glycal **5**[11] by Steglich acylation.[12] Reaction with 'diacetone glucose' **7** (DAG-H) in dichloromethane with iodonium dicollidinium perchlorate[13] as promoter afforded **8** in 65% yield ($\alpha:\beta = 6.7:1$). Similarly ester **10**, prepared from **9**,[14] afforded **11** in 57% yield ($\alpha:\beta = 4:1$).

Zamojski and coworkers[3c] have shown that 3,4,6-tri-*O*-acetyl-D-galactal, which exhibits anomalous behaviour under the standard conditions,[1] gives Ferrier rearrangement products under modified procedures.[3c] Accordingly the behaviour of glycal **13** was of interest. Reaction with **7** under our oxidative conditions gave a 1.7 : 1 mixture of **14** and **15** (70% yield). On the other hand the 3-epimer **16** (obtained in 85% yield from **12**,[15] by a Mitsunobu reaction[16] utilizing n-pentenoic acid) reacted with **7** to give **15** as a single product in 62% yield.

Table 1 Ferrier rearrangement of 3-*O*-pentenoyl glycals with IDCP as promotor



Reagents: i, Dicyclohexylcarbodiimide (1.2 equiv.), 4-*N*,*N*-dimethylaminopyridine (cat.), CH_2Cl_2, room temp., **6**, 80% yield; **10**, 94% yield; **13**, 86% yield; ii, PPh_3 (2 equiv.), n-pentenoic acid (2 equiv.), diisopropyl azodicarboxylate, toluene, room temp., 24 h, 85% yield. *Typical reaction procedure for glycoside coupling*: the C-3 n-pentenoylated glycal (1 equiv.) and alcohol donor (1 equiv.), azeotropically dried with toluene and kept under vacuum, were dissolved in dry CH_2Cl_2 (*ca.* 0.1 mmol ml^{-1}) under argon, and pulverised activated molecular sieves (4 Å) were added. Iodonium dicollidinium perchlorate (1.6 equiv.) was added and after TLC indicated that the glycal had been consumed, the reaction mixture was quenched with 10% sodium thiosulfate solution, followed by saturated sodium hydrogen carbonate and brine. Flash chromatography separation afforded the corresponding products. (Bn = $PhCH_2$).

An even more demanding example was the reaction of pentenoylated glycals **6** and **10** with highly hindered 1,3,4,6-tetra-*O*-acetyl-D-fructofuranose **17**.[17] Attempts in our laboratory to react triacetyl glucal and **17** under Ferrier conditions had been unsuccessful.[18] However in the present case, the disaccharides **18** and **19** were obtained in excellent yields. Compound **19** was a key intermediate in the first stereospecific synthesis of sucrose[13a,b] and, therefore, this methodology allows an expeditious approach to sucrose.

The mechanism proposed for the formation of disaccharides involves: (*a*) chemoselective attack by the electrophile at the terminal double bond (B) in **4** rather than at the electron-rich

enol ether[19] (A); (*b*) formation of an allylic oxo-carbenium ion **I** and (*c*) quenching at the anomeric position by the electrophile, R′OH. The α:β selectivity is similar to that of the Ferrier rearrangement. An additional point of interest is that further reaction of **2** is not expected to occur in view of the well documented resistance of hex-2-enopyranosides to reaction with electrophiles.[19a]

Anchimeric assistance, as claimed by Ferrier,[1] can be excluded in our case because of the use of non-participant protecting groups at C-4. Thus our results are in agreement with the rationalization of Zamojski *et al.* for the Ferrier rearrangement, which is based on the leaving properties of the group at C-3.[3c]

Our results also seem to indicate that the leaving group properties are reinforced when the anomeric oxygen lone pair is *anti* to the leaving group at C-3.

This oxidative modification of the Ferrier rearrangement allows the reaction to take place under non-acidic conditions and with fairly unreactive secondary and tertiary hydroxy groups of monosaccharides to afford coupling products in fairly good yields. Extension of this methodology to other glycosyl donors is underway and will be reported soon.

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