Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8259-8262, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01761-1

Phenolic Ferrier Reaction and Its Application to the Natural Product Synthesis.

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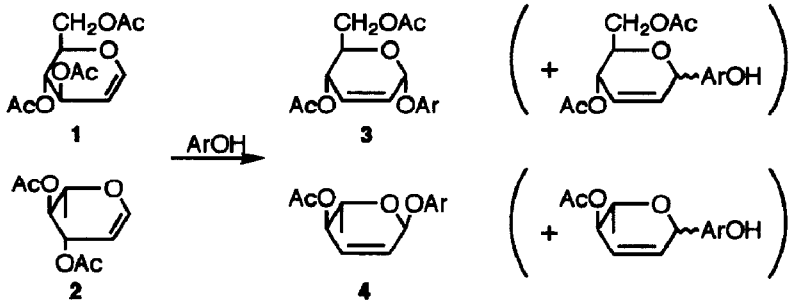
Abstract: Ferrier reaction between acetylglycals and phenols proceeded smoothly to give α-*O*- Δ^2- glycosides predominantly. The products were converted to bio-active natural products.

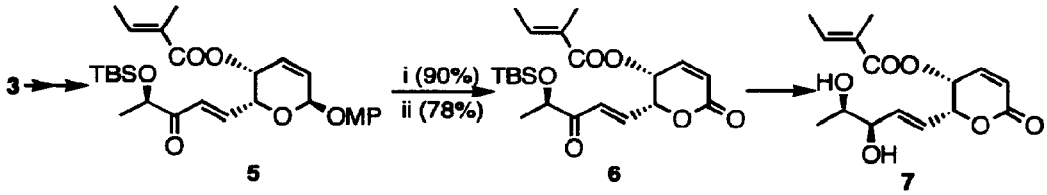
Ferrier reaction is known as a method to produce *O*-Δ^2-glycosides from glycal esters and hydroxy compounds.[1] This reaction is catalyzed by Lewis acid or heat. In spite of good yields of alkyl *O*-Δ^2-glycoside esters, aryl derivatives were obtained in poor yields by the catalysis of Lewis acid. Very recently, Sulikowski *et al* reported that aryl *O*-Δ^2-glycosides could not be obtained by the Ferrier reaction, but are obtained by Mitsunobu reaction *via* SN2' displacement.[2]

Aryl *O*-Δ^2-glycosides are regarded as hydrophilic derivatives of aromatic compounds as well as protected Δ^2-sugars because aryl moieties are expected to be oxidatively removed without affecting other functional groups.[3] In our studies on the application of Ferrier reaction products to the synthesis of natural products, we found the facile modification of the reaction condition to yield the aryl *O*-Δ^2-glycosides. We now report the method for the synthesis of aryl *O*-Δ^2-glycosides, an efficient oxidative removal of *p*-methoxyphenoxy group at C-1, and application of these reactions to the synthesis of bio-active natural products and related compounds.

At first 3,4,6-tri-*O*-acetylglucal **1** was treated with a slight excess amount of *p*-methoxyphenol in CH_2Cl_2 in the presence of 20 mol. % of $BF_3 \cdot Et_2O$. The product was a mixture of aryl α- and β-*C*-Δ^2-glycosides as also shown in the literature[1], and these types of compounds have different utilities.[4] However, lowering the amount of Lewis acid to 5 mol. % enabled to give aryl *O*-Δ^2-glycosides in good yields. As to catalysts examined, other Lewis acids as TMS triflate, silver perchlorate, stannic chloride or stannic bromide did not improve yields and/or stereoselectivity. Among the solvents for the reaction medium, toluene was found to be preferable to yield *O*-Δ^2-glycosides. This solvent effect was also observed in the case of 3,4-di-*O*-acetylrhamnal **2** as a substrate. As summarized in Table 1, the reaction with 5 mol. % of $BF_3 \cdot Et_2O$ in toluene at low temperature gave the best results. Though the product of each entry was a mixture of α- and β-*O*-Δ^2-glycosides (α/β = 10/1), pure α-isomer could be isolated by the simple recrystallization of the reaction product.



(Ar = *p*-methoxyphenyl, phenyl)



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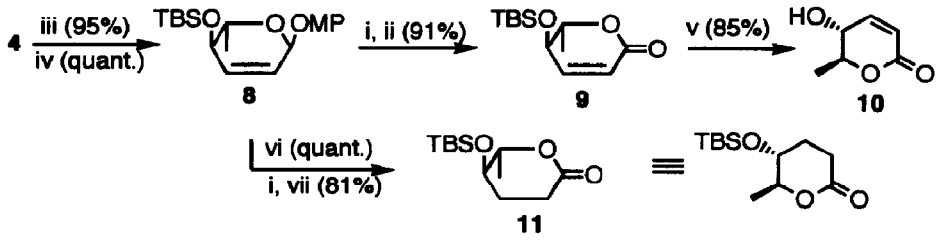

(MP = *p*-methoxyphenyl)

i, $Ag(DPAH)_2$ / aq.CH_3CN; ii, MnO_2 / CH_2Cl_2; iii, K_2CO_3 / MeOH; iv, TBS-Cl / imidazole / DMF; v, TBAF - AcOH; vi, H_2 / Pd-C; vii, PDC / DMF

Ferrier reaction products, **3** and **4**, were subjected to the following transformation by taking advantages of their stereochemistry. **3** (Ar = MP) was converted to **5** in 6 steps (i) hydrolysis of acetyl groups (quant.), ii) protection of C-6-hydroxy group as *t*-butyldiphenylsilyl (TBDPS) ether (94%), iii) esterification of C-4 hydroxy group under Mitsunobu's condition, iv) deprotection of C-6-TBDPS, v) Swern oxidation of C-6 hydroxy group (in 41 % yield for 3 steps) and vi) Wittig-Horner reaction at C-6 (57%)). To remove *p*-methoxyphenyl protective group, we first tried to oxidize with ceric ammonium nitrate (CAN).[7] But the yield of deprotected product was not satisfactory and reproducibility of the reaction was poor, because the substrate and product were partially decomposed in the strongly acidic reaction medium.

Table 1 Ferrier Reaction of Acetylglycals with Phenols.

acetylglycal	phenol	solvent	temp. / time (hr)	product	
				O-glycoside[5]	*C*-glycoside[6]
1	MPOH	CH_2Cl_2	-10°C / 1	-	72% (α/β = 3/4)
		toluene	r.t. / 1	12%	42% (α/β = 1/1)
			-10°C / 2	83% (α/β = 10/1)	17% (α/β = 1/1)
			-10°C / 2.5	92% (α/β = 10/1)*	-
	PhOH	toluene	-20°C ~ r.t. / 10	59% (α/β = 10/1)*	-
2	MPOH	toluene	-10°C / 5	97% (α/β = 10/1)*	
	PhOH	toluene	-5°C ~ r.t. / 5	57% (α/β = 20/1)*	

MPOH: *p*-methoxyphenol; PhOH: phenol.
Reaction condition: acetylglycal 3.7 mmol; phenol 4 mmol; $BF_3 \cdot Et_2O$ 0.8 mmol; solvent 30 ml.
*: 0.2 mmol of $BF_3 \cdot Et_2O$ was used.

On the other hand, silver (II) bis-(hydrogen dipicolinate) ($Ag(DPAH)_2$)[8] was found to be a mild and efficient oxidizing agent working in the weakly acidic medium and gave within 30 min the desired product in 90 % yield in aq.CH_3CN. Further oxidation with active manganese dioxide gave dihydropyranone **6**, which is a synthetic precursor for the enantiomer of phomopsolide B,[9] a mold metabolite with an antifeedand and antiboring activity against elm bark beetle.[10] **4** (Ar = MP) was converted to **8** by the conventional method. Then **8** was treated successively with $Ag(DPAH)_2$ in aq.CH_3CN and active manganese dioxide in CH_2Cl_2 to give dihydropyranone **9** in 91 % yield. Cleavage of *t*-butyldimethylsilyl (TBS) ether with tetrabutylammonium fluoride (TBAF) - acetic acid gave osmundalactone **10** (85 %), a fern metabolite with an antifeedant activity against larvae of butterfly.[11] A catalytic hydrogenation of **8** gave a quantitative yield of saturated acetal, which was treated successively with $Ag(DPAH)_2$ and pyridinium dichromate (PDC) in DMF to yield tetrahydropyranone **11** (81 %), an antipode of the synthon for the antibiotic aspyrone.[12]

As mentioned above,[13] it is noteworthy that an introduction of aryloxy group into anomeric centers of Δ^2-sugars and oxidative removal of *p*-methoxyphenoxy group with $Ag(DPAH)_2$ under mild condition are versatile and promising tools for the synthesis of aromatic derivatives and/or modified carbohydrates.

Acknowledgment: We thank ARC of Du Pont Japan Ltd. for financial support of this work.

References and Notes

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5. The ratio of α/β was estimated from NMR spectra of mixture of both isomers. $\delta_{1\text{-}H}$ ($CDCl_3$) for **3** (Ar = Ph) : 5.70 (α) and 5.81 (β). $\delta_{1\text{-}H}$ ($CDCl_3$) for **3** (Ar = MP) : 5.57 (α) and 5.70 (β).
6. The ratio of α/β was determined after acetylation and separation of each isomer by preparative TLC. $\delta_{1\text{-}H}$ ($CDCl_3$) for C-Δ^2-glycoside obtained from **1** and *p*-methoxyphenol : 5.27 (β) and 5.43 (α).
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13. The structure of each compound was confirmed by spectroscopic and elemental analyses. Selected physical constants were as follows:
    3 (Ar=Ph) : mp 50-51°C, $[\alpha]_D^{22}$ +167° (EtOH), +161° ($CHCl_3$), (lit.[1] $[\alpha]_D^{20}$ +131.7° (EtOH)); **3** (Ar=MP) : mp 78.5-79.5°C, $[\alpha]_D^{22}$ +178° ($CHCl_3$), (lit.[14] mp 77-77.5°C); **4** (Ar=Ph) : mp 65.5-66°C, $[\alpha]_D^{22}$ -190° ($CHCl_3$); **4** (Ar=MP) : mp 122.5-123°C, $[\alpha]_D^{22}$ -209.6° ($CHCl_3$); **10**: mp 82-82.5°C, $[\alpha]_D^{22}$ -71.7° (H_2O), (lit.[11a] mp 82.5°C, $[\alpha]_D^{20}$ -70.3° (H_2O), lit.[11b] mp 82-82.5°C, $[\alpha]_D^{20}$ -70.6° (H_2O)); **11**: mp 68.5-69.5°C, $[\alpha]_D^{22}$ -73.0° ($CHCl_3$), (for antipode, lit.[12] mp 68-69°C, $[\alpha]_D^{21}$ +74.6° ($CHCl_3$)).
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(*Received in Japan* 13 *July* 1994)