

A 1,2-*O-O*-SILYL-MIGRATION-CLAISEN-REARRANGEMENT-S_N2'-
DISPLACEMENT SEQUENCE IN THE STEREOSELECTIVE SYNTHESIS
OF 5-OXAPROSTANOID DERIVATIVES

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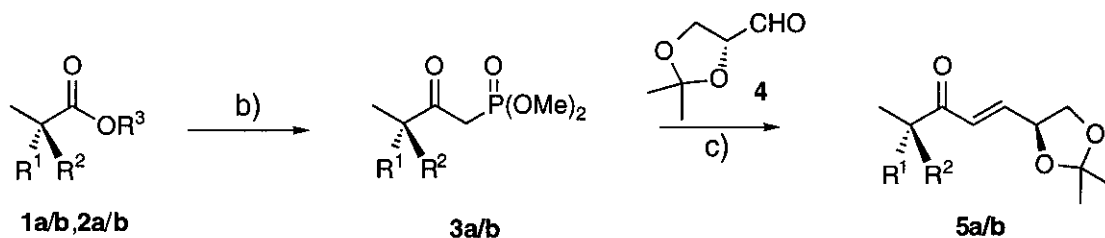
Dedicated to Prof. R. Huisgen on the occasion of his 75th birthday.

Abstract- A novel stereocontrolled route to 5-oxaprostaglandin and PGF intermediates is described, which starts from the ene-diols (**6/7**) and uses a sequence of Claisen rearrangement, 1,2-*O-O*-silyl migration and S_N2'-cyclization reactions (**9b** → **10a/b** via **11a/b**).

The synthesis of prostanoid derivatives has been a main topic for many years.¹ 5-Oxaprostanoids have, despite their interesting pharmacological properties, been prepared only in a few cases, on relatively long routes.² We describe here a novel and facile access to these compounds, employing a Claisen-rearrangement followed by a S_N2'-cyclization to form the tetrahydrofuran ring as the key steps.

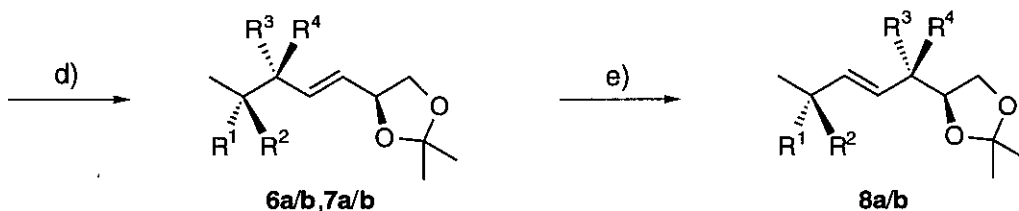
Our synthesis starts from the (*R*)- and (*S*)-lactic esters (**1a/b**), which were converted into the configurationally stable ketophosphonates (**3a/b**). After deprotonation **3a** and **3b** were olefinated with (*R*)-2,3-isopropylidene glyceraldehyde (**4**) to the keto olefins (**5a/b**). The reduction of the carbonyl function with L-selectride proceeded diastereoselectively (>99:1) under reversible 1,2-migration of the silyl protective group to give a 60:40 (55:45)-mixture of the regioisomeres (**6a/7a**) and (**6b/7b**), respectively. Without separation these mixtures were submitted to a Claisen-Eschenmoser-rearrangement,³ and to our surprise, the material was

quantitatively transformed into the γ,δ -unsaturated amides (**8a**) and (**8b**). Obviously a mobile equilibrium between **6a/7a** and **6b/7b** is established from which **6a** and **7a** are removed by the irreversible rearrangement!



	R ¹	R ²	R ³
1a	H	OH	Et
2a	H	OTBDPS	Et
1b	OH	H	iBu
2b	OTBDPS	H	iBu

	R ¹	R ²
3a/5a	H	OTBDPS
3b/5b	OTBDPS	H



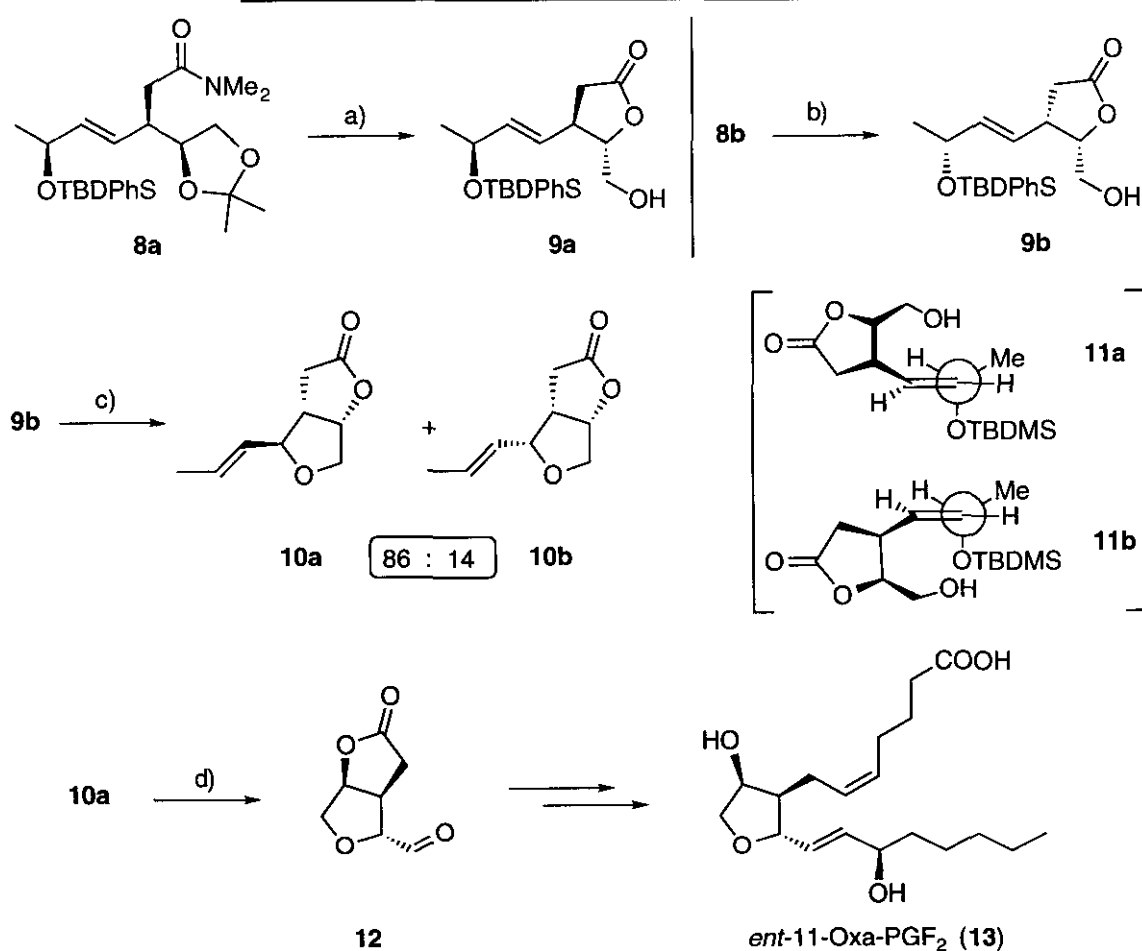
	R ¹	R ²	R ³	R ⁴
6a	H	OTBDPS	H	OH
7a	H	OH	H	OTBDPS
6b	OTBDPS	H	OH	H
7b	OH	H	OTBDPS	H

	R ¹	R ²	R ³	R ⁴
8a	H	OTBDPS	H	CH ₂ CONMe ₂
8b	OTBDPS	H	CH ₂ CONMe ₂	H

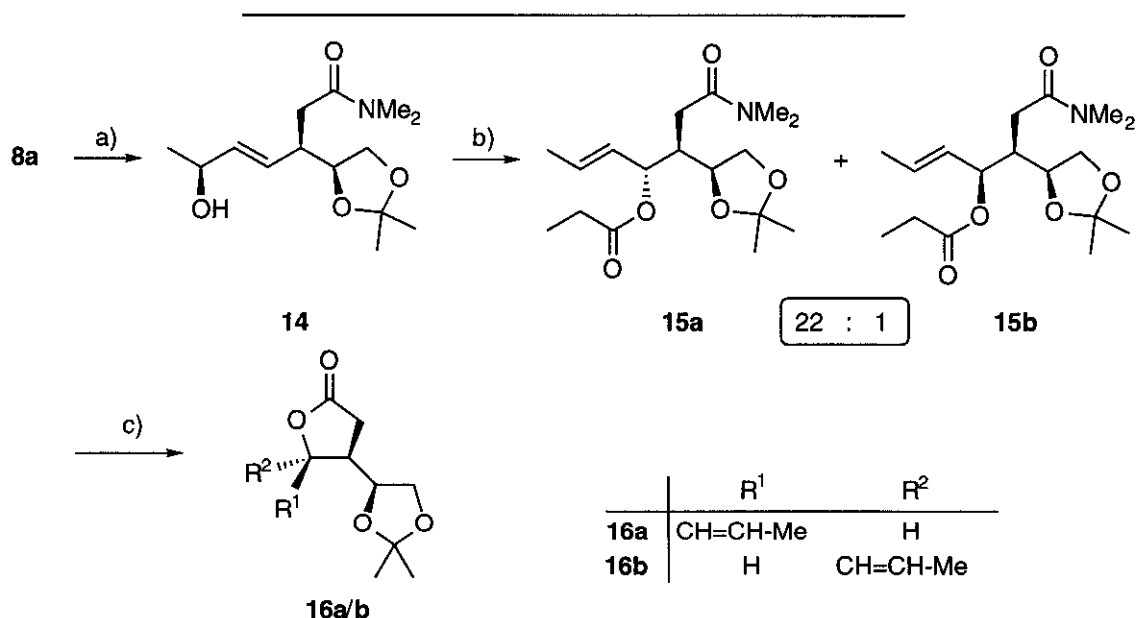
a): tBuPh₂SiCl, imidazole, DMF, 50 °C, 18 h, 98%; b): CH₃P(O)(OMe)₂/n-BuLi, Et₂O, -78 °C, 7 h, 97%; c): LDA, Et₂O, -78 °C; **4**, -78 °C, 2 h, 79%; d): L-Selectride, THF, -78 °C, 16 h, 87%; e): MeC(OMe)₂NMe₂, toluene, 95 °C, 6 h, 98%

Acid catalyzed opening of the acetonide ring led to the γ -lactones (**9a/b**) whose configurations were determined by DNOE spectroscopy. The all-*syn* diastereomer (**9b**) was treated with trifluoroacetic acid, which resulted in a clean S_N2'-displacement of the OTBDPS-group and formation of the tetrahydrofuran ring to give the two stereoisomers (**10a/b**) in a ratio of 86:14, according to hplc-analysis. This means that the displacement has proceeds via an *anti*-periplanar transition state (**11a**) preferentially, and that the *syn*-periplanar arrangement

(11b) is clearly disfavored.⁴ Olefin (10a) may be converted *via* aldehyde (12) to 5-oxaprostaglandins, such as 13, by standard methodology.¹



A highly stereocontrolled *anti*-periplanar S_N2'-rearrangement is observed, if allylic alcohol (14), readily obtained from 8a by desilylation, is treated with propionic acid and trimethyl orthoformate. In this case the diastereomers (15a/b) are obtained in a ratio of 22:1! Base induced deacylation leads to the γ -lactones (16a/b), whose relative configurations were determined by DNOE measurements. 16a is a useful intermediate in the synthesis of PGF_{2 α} and its derivatives.⁵



a): TBAF, THF, 25 °C, 16 h, 97%; b): HC(OMe)₃, EtCO₂H, 140 °C, 18 h, 94%; c): K₂CO₃, MeOH/H₂O, 20 °C, 16 h, 92%.

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