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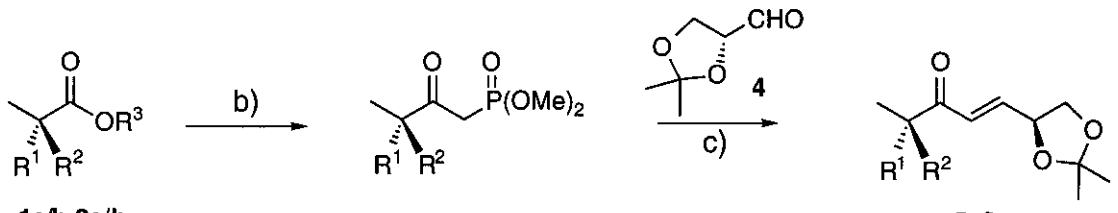
Dedicated to Prof. R. Huisgen on the occasion of his 75th birthday.

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

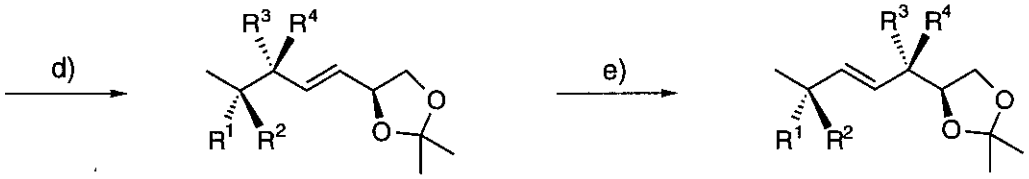
quantitatively transformed into the γ,δ-unsaturated amides (**8a**) and (**8b**). Obviously a mobile equilibrium between **6a/7a** and **6b/7b** is established from which **6a** and **7a** are removed by the irreversible rearrangement!



1a/b,2a/b **3a/b** **5a/b**

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

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



6a/b,7a/b **8a/b**

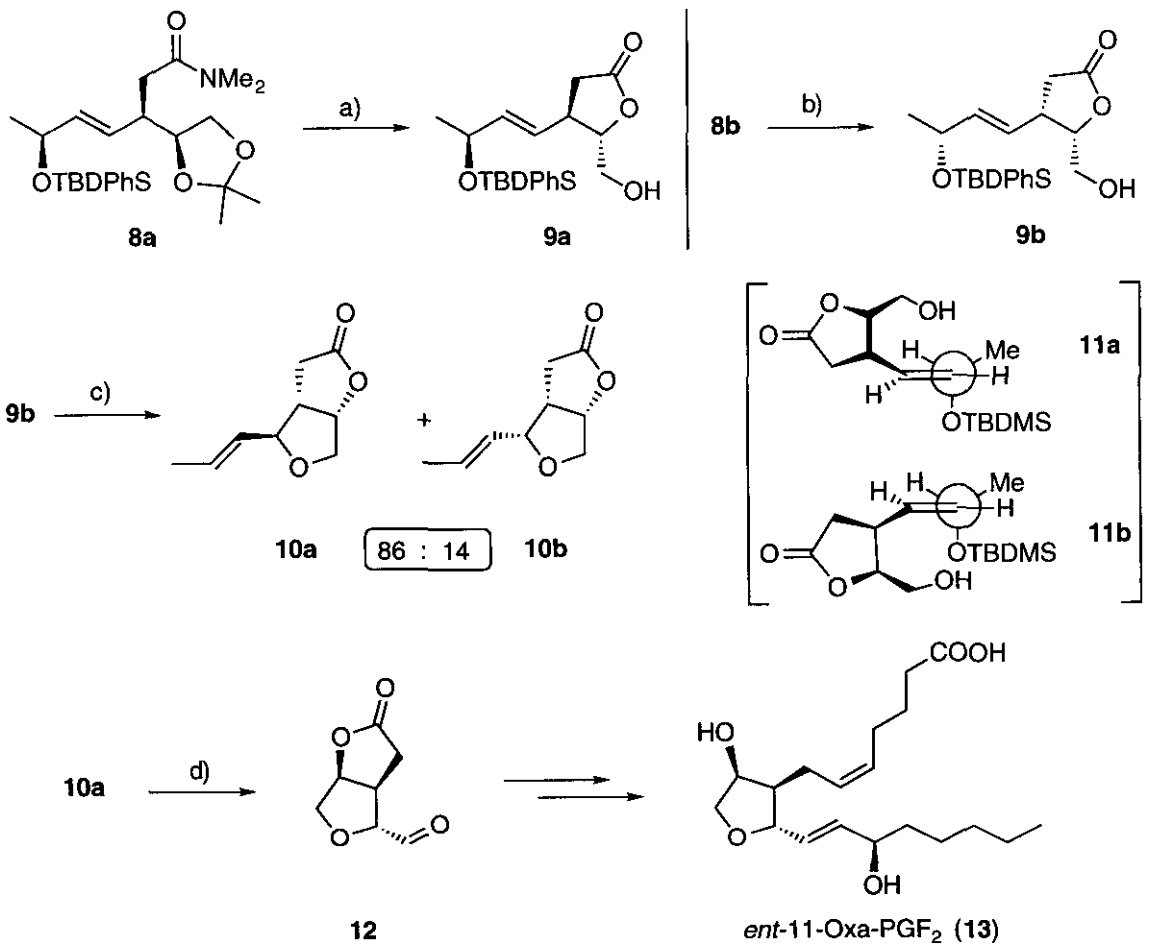
	R^1	R^2	R^3	R^4
6a	H	OTBDPS	H	OH
7a	H	OH	H	OTBDPS
6b	OTBDPS	H	OH	H
7b	OH	H	OTBDPS	H

	R^1	R^2	R^3	R^4
8a	H	OTBDPS	H	CH_2CONMe_2
8b	OTBDPS	H	CH_2CONMe_2	H

a): $tBuPh_2SiCl$, imidazole, DMF, 50 °C, 18 h, 98%; b): $CH_3P(O)(OMe)_2$/*n*-BuLi, Et_2O, -78 °C, 7 h, 97%; c): LDA, Et_2O, -78 °C; **4**, -78 °C, 2 h, 79%; d): L-Selectride, THF, -78 °C, 16 h, 87%; e): $MeC(OMe)_2NMe_2$, toluene, 95 °C, 6 h, 98%

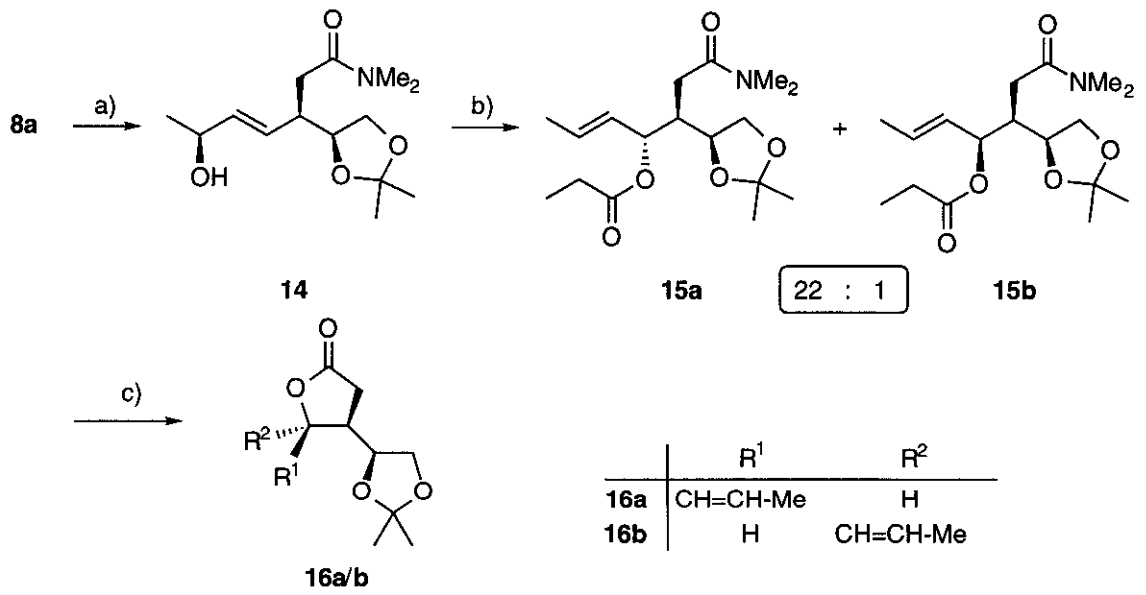
Acid catalyzed opening of the acetonide ring led to the γ-lactones (**9a/b**) whose configurations were determined by DNOE spectroscopy. The all-*syn* diastereomer (**9b**) was treated with trifluoracetic acid, which resulted in a clean S_N2'-displacement of the OTBDPS-group and formation of the tetrahydrofuran ring to give the two stereoisomeres (**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): 80% AcOH, 50 °C, 6 h, 91%; b): 60% AcOH, 60 °C, 2 d, 79%; c): TFA, CH_2Cl_2, 50 °C, 18 h, 87%; d): O_3, PPh_3.

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 $PGF_{2\alpha}$- and its derivatives.[5]



a): TBAF, THF, 25 °C, 16 h, 97%; b): $HC(OMe)_3$, $EtCO_2H$, 140 °C, 18 h, 94%; c): K_2CO_3, $MeOH/H_2O$, 20 °C, 16 h, 92%.

REFERENCES

1. B. Riefling, *Kontakte (Merck),* **1983**, 26 and **1984**, 50; R.F. Newton and S.M. Roberts, *Synthesis,* **1984**, 449; P.W. Collins and S.W. Djuric, *Chem. Rev.*, **1993**, *93*, 1533.

2. G.J. Lourens and J.M Koekemoer, *Tetrahedron Lett.,* **1975**, 3715 and 3719; I.T. Harrison. V.R. Fletcher,and J.H. Fried, *ibid.,* **1974**, 2733; I. Vlattas, A. Ong Lee, *ibid.,* **1974**, 4451; S. Hanessian, P. Dextrase, A. Fourgerousse,and Y. Guindon, *ibid.,* **1974**, 3983; Review: J.S. Bindra and R. Bindra, *Prostaglandin Synthesis*, Academic Press, New York, **1977**.

3. A.E. Wick, D. Felix, K. Steen.and A. Eschenmoser, *Helv. Chim. Acta,* **1964**, *47*, 2425.

4. E.J. Corey and N.W. Boaz, *Tetrahedron Lett.,* **1984**, *25*, 3063; J.M. Klunder and G.H. Posner in *"Comprehensive Organic Synthesis," Vol. 3* (ed. B.M. Trost), Pergamon Press, Oxford, **1990**, 217; A. Yanagisawa, Y. Noritake, N. Nomura,and H. Yamamoto, *Synlett,* **1991**, 251; A. Yanagisawa, N. Nomura, Y. Noritake,and H. Yamamoto, *Synlthesis,* **1991**, 1130; A. Yanagisawa, N. Nomura,and H. Yamamoto, *Synlett,* **1993**, 689; G. Funk, *PhD-Thesis*, Freie Universität, Berlin, **1991**.

5. G. Stork and G. Kraus, *J. Am. Chem. Soc.*, **1976**, *98*, 1285.

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