STEREOCONTROLLED FORMATION OF FUNCTIONALIZED *ERYTHRO*-1,2-DIOLS *VIA* HYDROBORATION OF 2-ALKYL-4,5-DIHYDROFURANS

Roger Amouroux*, Abdelmalik Slassi and Christine Saluzzo

Laboratoire de Chimie Organique Physique et Synthétique, associé au CNRS. Université Claude Bernard, Lyon I, 43 Boulevard du 11 Novembre 1918, 69622 VILLEURBANNE (France)

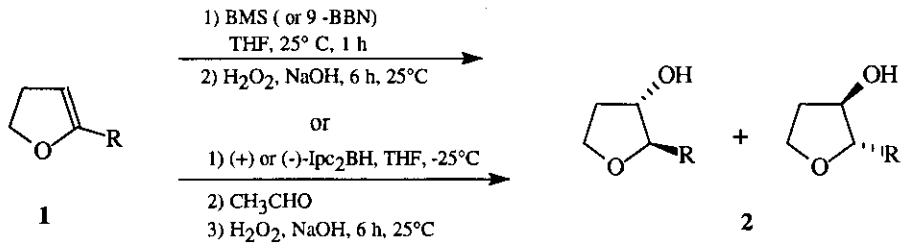
Abstract - *trans*-2-Alkyl-3-hydroxytetrahydrofurans, prepared by the stereospecific hydroboration / oxidation reaction of 2-alkyl-4,5-dihydrofurans, were regioselectively cleaved with $(CH_3)_3SiCl$ / NaI to afford 1-iodo-*erythro*-3,4-diols in CH_3CN or the corresponding acetonide derivatives in CH_3COCH_3.

The synthesis of stereochemically defined substituted tetrahydrofurans and the subsequent opening of these heterocycles give access to acyclic polyfunctional building blocks useful in the synthesis of natural products .[1,2] This methodology requires preparation of tetrahydrofurans with good stereochemical control and, in addition, a highly regioselective method for cleavage of the cyclic ether.

In this work, we report the regio- and stereoselective hydroboration / oxidation of 2-alkyl-4,5-dihydrofurans[3,4] followed by the regioselective ring opening of the resulting *trans*-2-alkyl-3-hydroxytetrahydrofurans with $(CH_3)_3SiCl$ / NaI .[5] The combination of these two reactions constitutes an efficient synthesis of isomerically pure *erythro*-1,2-diols bearing a primary iodine atom useful for further functionalizations .[6]

The 2-alkyl-4,5-dihydrofurans (**1b-e**) used in this study were prepared by lithiation / alkylation of 2,3-dihydrofuran (**1a**) according to published procedures.[8] Dihydrofurans (**1a-e**) were treated with the borane-methyl sulfide complex (BMS, 0.33 molar equiv.) or with 9-borabicyclononane (9-BBN, 1 equiv.) in THF at 25° C for 1 h .[4] The resulting trialkylboranes were then oxidized (H_2O_2, NaOH) to afford *trans*-2-alkyl-3-hydroxytetrahydrofurans (**2**) in good yields (Table 1) .[9] Similar results were obtained with both hydroborating agents. As previously reported [4] for **1b** (R = CH_3), the hydroboration occurred exclusively at the C3 position

of the heterocycle and gave stereoselectively the *trans* diastereoisomer (Scheme 1). Stereochemical homogeneity of the products was revealed by gc and confirmed by ^{13}C-nmr.



Scheme 1

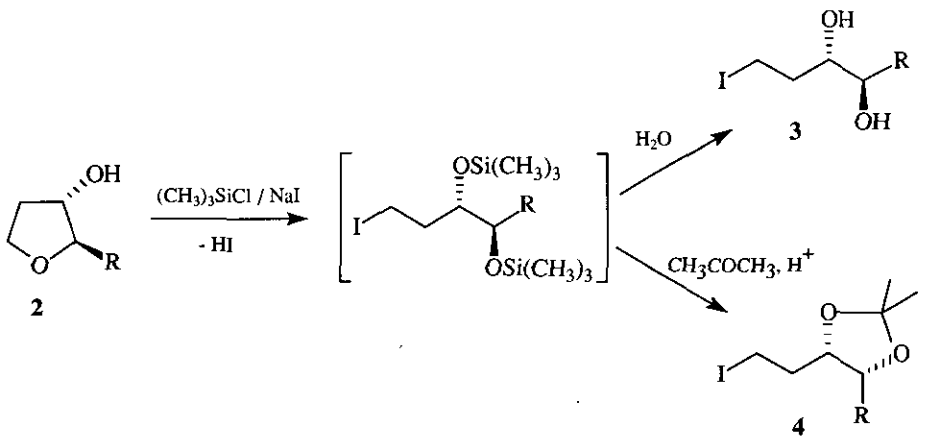
Table 1 : Hydroboration of 2-alkyl-4,5-dihydrofurans (**1**) in THF

DHF	R	Reagent	Time (h)	Temperature(°C)	Yield of **2** [a] (%)	$[\alpha]_D$ [b]	% ee (config.)
1a	H	BMS	1	25	71	-	-
		9-BBN	1	25	73	-	-
1b	CH_3	BMS	1	25	77	-	-
		9-BBN	1	25	64	-	-
		(+)Ipc_2BH	24	-25	68	-28.9°	72 (2S, 3R)
		(-) Ipc_2BH	24	-25	65	+29.0°	72 (2R, 3S)
1c	C_2H_5	BMS	1	25	75	-	-
		9-BBN	1	25	75	-	-
1d	nC_5H_{11}	BMS	1	25	75	-	-
		9-BBN	1	25	73	-	-
		(+)Ipc_2BH	36	-25	62	- 46.4°	70 (2S, 3R)
		(-) Ipc_2BH	36	-25	60	+46.5°	70 (2R, 3S)
1e	$nC_{10}H_{21}$	BMS	1	25	81	-	-
		9-BBN	1	25	74	-	-

a) Isolated yields after column chromatography (SiO_2, hexane - ether 9 : 1)
b) Optical rotations were measured in CH_3OH (c = 1)

We also examined the possibility of asymmetric hydroboration by using (+)- or (-)-diisopinocampheylborane (Ipc_2BH). Brown *et al.* [7] have shown that these reagents gave good asymmetric induction with dihydrofuran (100% ee) and dihydropyran (86% ee), but their use with 2-substituted dihydrofurans has not yet been reported. Interestingly, these substrates led to the simultaneous formation of two asymmetric centers. We performed the hydroboration of 2-alkyldihydrofurans (**1b**) (R = CH_3) and (**1d**) (R = nC_5H_{11}) with (+)-Ipc_2BH and (-)-Ipc_2BH

prepared from (-)-α-pinene and (+)-α-pinene, respectively.[10] The procedure described for the unsubstituted dihydrofuran[7] was used with longer reaction times. Treatment of the trialkylboranes with acetaldehyde and subsequent oxidation of the resulting boronates with alkaline H_2O_2 afforded *trans*-2-alkyl-3-hydroxytetrahydrofurans (**2b**) and (**2d**) in 60 to 68% yield (Table 1). The enantiomeric excess (ee) of **2b** and **2d** (Table 1) was estimated by ^{19}F-nmr (75 MHz) analysis of the corresponding Mosher esters. Absolute configuration of these compounds was attributed by comparison with products of known configuration obtained by an independant route from S-malic acid.[11]



Scheme 2

Finally, we studied the behaviour of 2-alkyl-3-hydroxytetrahydrofurans in the ring opening reaction.The tetrahydrofuran ring in racemic compounds (**2a-d**) were regioselectively opened at room temperature in CH_3CN with trimethylsilyl iodide (2 equiv.) generated *in situ* by the reaction of trimethylsilyl chloride with NaI (Scheme 2). After silylation of the hydroxyl group, the cleavage was presumably initiated by electrophilic attack of silicon (from $(CH_3)_3SiI$) or of proton (from HI) on oxygen to give oxonium intermediates. These species then underwent ring opening by nucleophilic attack of iodide at the less substituted carbon to afford, after aqueous work-up, 1-iodo-*erythro*-3,4-diols (**3**) in 50-55% yields (Table 2). The modest yields observed, probably owing to the instability of the resulting iododiols, led us to explore some modifications of reaction conditions. Thus, we found it more convenient to carry out the reaction in acetone in order to form *in situ* the more stable iodoacetonides (**4**).[12] This offered advantages of better yields, easier work-up and purification and direct protection of the diol allowing further transformations of the iodo group .[2a]

Table 2 : Ring opening of 2-alkyl-3-hydroxytetrahydrofurans (**2**) with $(CH_3)_3SiCl$ / NaI [a)]

THF	R	Solvant	Products	Isolated yield (%)[b]
2a	H	CH_3COCH_3	**4a**	70
2b	CH_3	CH_3CN	**3b**	52
		CH_3COCH_3	**4b**	67
2c	C_2H_5	CH_3CN	**3c**	54
		CH_3COCH_3	**4c**	70
2d	nC_5H_{11}	CH_3COCH_3	**4d**	75

a) Reactions were carried out at room temperature for 5 h in CH_3CN and 10 -12 h in CH_3COCH_3

b) All compounds have been characterized by ir, ms, ^1H- and ^{13}C-nmr spectroscopy

In conclusion, this method affords an easy access to stereochemically pure functionalized 1,2-diols through two stereo- and regiochemically controlled reactions.

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9. The disubstituted tetrahydrofurans (**2**) were obtained along with 10-15% combined yields of acyclic 1,3- and 1,4-diols ($HOCH_2CH_2CHOHCH_2R$ and $HOCH_2CH_2CH_2CHOHR$). These compounds were formed

via a borane catalyzed elimination/ring cleavage reaction giving rise to an homoallylic alcohol derivative which was subsequently rehydroborated to afford, after oxidation, the observed diols. See ref. 3 and 4 for a detailed mechanism of this secondary reaction.

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12. A representative ring opening procedure is as follows:

To a solution of NaI (40 mmol, 6.0 g) in 50 ml of dry acetone were added, at room temperature, a solution of 20 mmol (2.04 g) of 3-hydroxy-2-methyltetrahydrofuran (**2b**) in 20 ml of acetone and then, dropwise, 40 mmol (5.1 ml) of $(CH_3)_3SiCl$. The mixture was stirred at room temperature for 10 h, then concentrated under reduced pressure, poured into a saturated $NaHCO_3$ solution (30 ml) and extracted with ether (3 x 30 ml). The combined organic extracts were decolorized using a solution of $Na_2S_2O_3$, washed with a saturated solution of NaCl until neutrality, dried over $MgSO_4$ and concentrated to give the crude product. Purification by chromatography through silica gel with 5% ether in hexane gave 3.6 g (67%) of the *erythro*-iodoacetonide (**4b**) as a colorless liquid. ^{1}H-Nmr ($CDCl_3$, 300 MHz) δ (ppm) 1.17 (d, J = 6.4 Hz, CH_3) ; 1.34 (s, CH_3) ; 1.43 (s, CH_3) ; 1.70-2.10 (m, CH_2) ; 3.20-3.40 (2m, CH_2I) ; 4.08-4.15 (m, CH) ; 4.25-4.34 (m, CH) ; ^{13}C nmr ($CDCl_3$, 75 MHz) δ (ppm) 2.65 (CH_2-I) ; 15.16 (CH_3) ; 25.74 (CH_3) ; 28.47 (CH_3) ; 34.22 (CH_2) ; 73.14 (CH) ; 77.60 (CH) ; ms, m/z(%), 255 (M^+ - 15, 33) ; 43 (100).

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