

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

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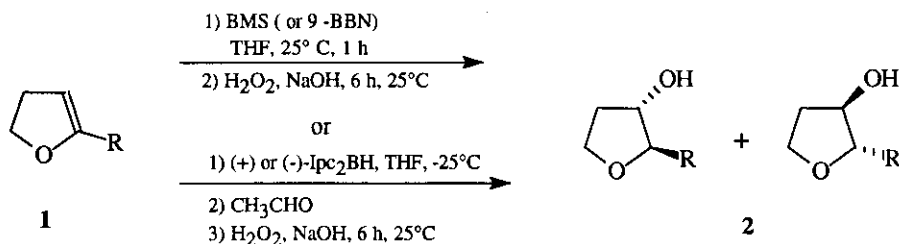
Abstract - *trans*-2-Alkyl-3-hydroxytetrahydrofurans, prepared by the stereospecific hydroboration / oxidation reaction of 2-alkyl-4,5-dihydrofurans, were regioselectively cleaved with $(\text{CH}_3)_3\text{SiCl}$ / NaI to afford 1-iodo-*erythro*-3,4-diols in CH_3CN or the corresponding acetonide derivatives 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 $(\text{CH}_3)_3\text{SiCl}$ / 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 reported⁴ 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

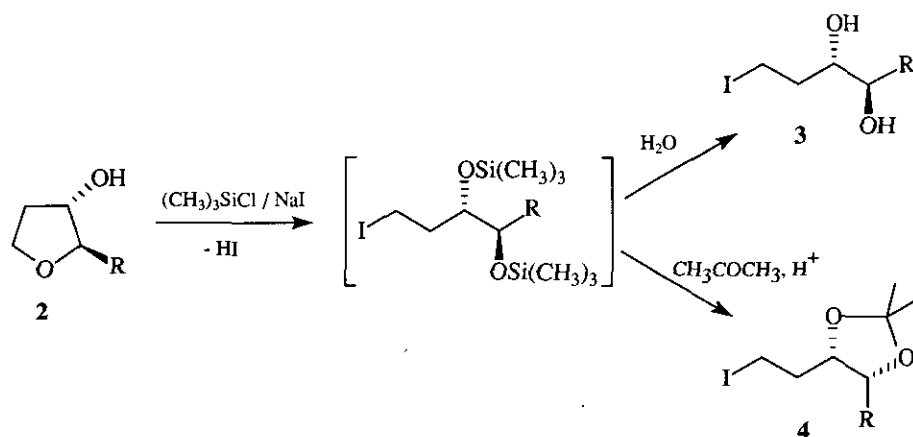
DHF	R	Reagent	Time (h)	Temperature(°C)	Yield of 2 ^a (%)	$[\alpha]_D^{25}$ ^b	% ee (config.)
1a	H	BMS	1	25	71	-	-
		9-BBN	1	25	73	-	-
1b	CH ₃	BMS	1	25	77	-	-
		9-BBN	1	25	64	-	-
		(+)-Ipc ₂ BH	24	-25	68	-28.9°	72 (2S, 3R)
		(-)-Ipc ₂ BH	24	-25	65	+29.0°	72 (2R, 3S)
1c	C ₂ H ₅	BMS	1	25	75	-	-
		9-BBN	1	25	75	-	-
1d	nC ₅ H ₁₁	BMS	1	25	75	-	-
		9-BBN	1	25	73	-	-
		(+)-Ipc ₂ BH	36	-25	62	-46.4°	70 (2S, 3R)
		(-)-Ipc ₂ BH	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 (SiO₂, hexane - ether 9 : 1)

b) Optical rotations were measured in CH₃OH (c = 1)

We also examined the possibility of asymmetric hydroboration by using (+)- or (-)-diisopinocampheylborane (Ipc₂BH). 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 = CH₃) and (1d) (R = nC₅H₁₁) with (+)-Ipc₂BH and (-)-Ipc₂BH

prepared from (-)- α -pinene and (+)- α -pinene, respectively.¹⁰ The procedure described for the unsubstituted dihydrofuran⁷ 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 independent 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 $(\text{CH}_3)_3\text{SiI}$) 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 iodoacetones (**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 $(\text{CH}_3)_3\text{SiCl} / \text{NaI}$ ^{a)}

THF	R	Solvent	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.

REFERENCES AND NOTES

- Y. Guindon, C. Yoakim, M. A. Bernstein, and H. E. Morton, *Tetrahedron Lett.*, 1985, **26**, 1185.
 - Y. Guindon, Y. St Denis, S. Daigneault, and H. E. Morton, *Tetrahedron Lett.*, 1986, **27**, 1237.
- M. Jatczak, R. Amouroux, and M. Chastrette, *Tetrahedron Lett.*, 1985, **26**, 2315.
 - R. Amouroux and S. Ejjiyar, *Tetrahedron Lett.*, 1991, **32**, 3059.
- G. Zweifel and J. Plamondon, *J. Org. Chem.*, 1970, **35**, 898.
- H. C. Brown, J. V. N. Vara Prasad, and Sheng-Hsu Zee, *J. Org. Chem.*, 1985, **50**, 1582.
- R. Amouroux, M. Jatczak, and M. Chastrette, *Bull. Soc. Chim. Fr.*, 1987, **II**, 505.
- J. E. Nystrom, T. D. Mc Canna, P. Helquist, and R. Amouroux, *Synthesis*, 1988, 56.
- H. C. Brown and J. V. N. Vara Prasad, *J. Am. Chem. Soc.*, 1986, **108**, 2049.
- P. J. J. M. Van Ool and H. M. Buck, *Recl. Trav. Chim. Pays-Bas*, 1984, **103**, 119.
 - R. K. Boeckman and K. J. Bruza, *Tetrahedron Lett.*, 1977, **18**, 4187.
- The disubstituted tetrahydrofurans (**2**) were obtained along with 10-15% combined yields of acyclic 1,3- and 1,4-diols ($\text{HOCH}_2\text{CH}_2\text{CHOHCH}_2\text{R}$ and $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CHOHR}$). 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.

10. H. C. Brown and B. Singaram, *J. Org. Chem.*, 1984, **49**, 945.
11. M. Thiam, A. Slassi, F. Chastrette, and R. Amouroux, *Synth. Comm.*, 1992, **22**, 83.
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 $(\text{CH}_3)_3\text{SiCl}$. 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 $\text{Na}_2\text{S}_2\text{O}_3$, 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*-iodoacetone (**4b**) as a colorless liquid. $^1\text{H-Nmr}$ (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); $^{13}\text{C nmr}$ (CDCl_3 , 75 MHz) δ (ppm) 2.65 ($\text{CH}_2\text{-I}$); 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 ($\text{M}^+ - 15$, 33); 43 (100).

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