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Facile determination of the diastereoisomeric purity of 2,3-pinanediol (1-chloroalkyl)boronates. Isolation of boronic esters containing a configurationally stable boron atom

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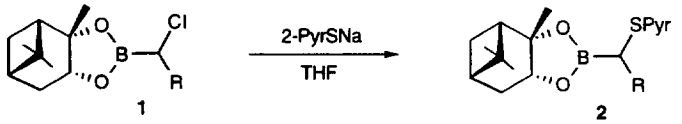
Abstract: The synthesis of [1-(2-pyridylthio)alkyl]boronic esters was explored as a means of determining the diastereoisomeric purity and the absolute configuration of the carbon α to the boron of the corresponding 1-chloroalkyl derivatives. The significant nonequivalences observed in the ^{1}H NMR spectra of the two diastereoisomers were attributed to the presence of a strong intramolecular nitrogen–boron coordination. Rigorous proof of a cyclic configurationally stable structure and determination of the boron configuration were obtained by X-ray crystallographic analysis. © 1997 Elsevier Science Ltd

Pinanediol (1-chloroalkyl)boronates **1** have been shown to play an important role in asymmetric synthesis and very promising results have been reported in the field of pheromones, polyols and α-amino boronic acids.[1] An accurate and reliable procedure for the determination of the diastereoisomeric purity of these versatile intermediates is therefore essential. (1-Chloroalkyl)boronic esters can be sometimes directly analysed as a result of the Δδ of a pinanyl proton (a doublet near 1.1–1.2 ppm).[2] However, this difference is often slight and, in this zone, overlapping peaks may prevent a precise measurement. Another reported analytical method was based on their conversion to the 1-acetamido derivatives and the measurement of the relative integrations of the broad NH peaks by ^{1}H NMR.[3] We here report an alternative simple and more general method based on the conversion of the boronic esters **1** to the 2-pyridylthio derivatives **2** (Scheme 1).



1 **2**

Scheme 1.

2 were easily prepared by reaction of the corresponding (1-chloroalkyl)boronic esters with sodium 2-pyridylthiolate in THF.[4] As illustrated for **2a** (R=Hex) (Figure 1), distinct chemical shifts were observed in the ^{1}H NMR spectra for two characteristic protons H_a (4.1–4.5 ppm) and H_b (8.2–8.5 ppm) that provided a convenient internal check on the correctness of the method. The diastereoisomeric purity can be accurately measured and no kinetic resolution has been observed. Integration of signals corresponds to 1/1 when starting from an equimolar mixture of diastereoisomers **1a**.[5] We also verified that there was no partial epimerization during the boron-assisted deplacement of the secondary chloride.[6]

A series of compounds **2** have been then prepared[7] and analysed by ^{1}H NMR spectroscopy[8] In all cases, the diastereoisomeric pairs of boronic esters exhibit typical differences between 0.16 and 0.30 ppm for H_a and 0.11 and 0.16 ppm for H_b (Table 1). The ^{11}B NMR spectra of **2** showed single peaks in the range 13 to 15 ppm consistent with a tetrahedral stereogenic boron resulting from an intramolecular

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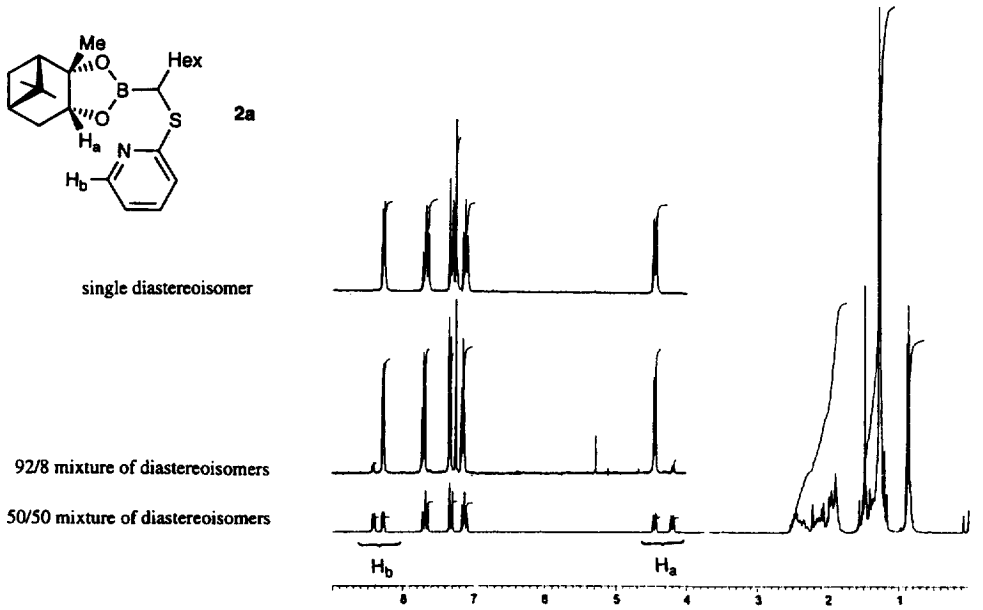
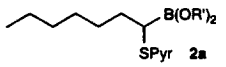
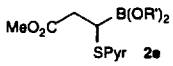
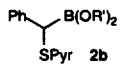
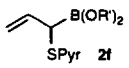
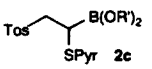
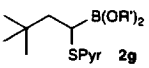
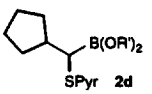
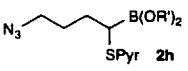


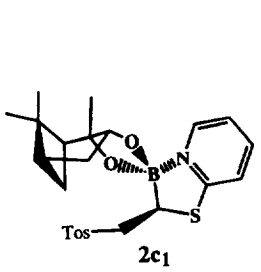
Figure 1. ^{1}H NMR (200 MHz) spectra of [1-(2-pyridylthio)heptyl]boronic ester **2a** in $CDCl_3$.

Table 1. ^{1}H NMR chemical shift differences $\Delta\delta$ (ppm) of some (+)-pinanediol boronates **2**

Entry	Boronates **2**	H_a	H_b	Entry	Boronates **2**	H_a	H_b
1		0.26	0.12	5		0.24	0.13
2		0.16	0.11	6		0.16	0.11
3		0.18	0.11	7		0.26	0.14
4		0.30	0.16	8		0.26	0.14

boron–nitrogen chelation.[9,10] We succeeded in isolating by crystallization two pure non racemic [1-(2-pyridylthio)alkyl] boronic esters **2** ($\mathbf{a_1}$, R=Hex and $\mathbf{c_1}$, R=CH_2Tos). These compounds showed a single set of signals in ^{1}H and ^{13}C NMR,[11] thus indicating that the stereogenic boron was configurationally stable in $CDCl_3$ solution. Rigourous proofs of the cyclic structure and determination of the absolute configurations, *S* at boron and *R* at carbon α to SPyr, were obtained by X-ray crystallographic analysis of $\mathbf{2c_1}$ (Figure 2).[12] This clearly shows a short nitrogen–boron bond of 1.66 Å and also confirms that attack by the nitrogen of the pyridyl group exclusively occurred on the less hindered face of the boronate ring.[13]

^{1}H NMR data of $\mathbf{2c_1}$ were in agreement with those of other boronates **2** prepared from scalemic chloro compounds **1**.[14] Useful NMR configurational correlation can then be devised that permit the assignment of the absolute stereochemistry of a (1-chloroalkyl)boronic ester **1**. A 1(*S*) configuration



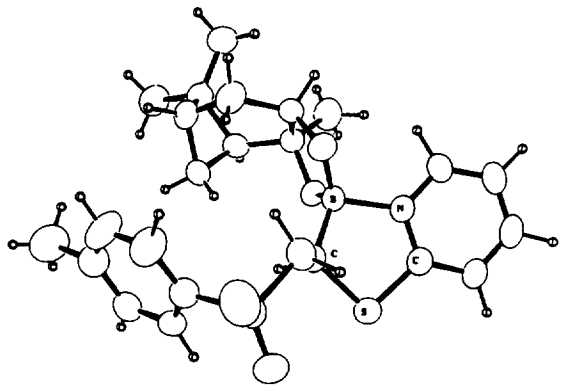


Figure 2. ORTEP drawing of the X-ray structure of $2c_1$.

of the carbon α to the boron in **1** corresponds to a higher chemical shift for H_a and a lower chemical shift for H_b in the ^1H NMR spectrum of **2**.

1,2-Dicyclohexyl-1,2-ethanediol is also an excellent chiral director in the homologation reaction,[1] but, in this series, there is no suitable marker for the evaluation of the ratio of the diastereoisomeric (1-halogenoalkyl)boronic esters.[15] Although the difference is significantly smaller than in the case of pinanediol, 2-pyridylthio derivatives are still convenient for the determination of the diastereoisomeric purity since we measured a $\Delta\delta$=0.04 ppm for H_b in the 500 MHz spectrum of 1,2-dicyclohexyl-1,2-ethanediol 1-(2-pyridylthio)heptane-1-boronate.

Acknowledgements

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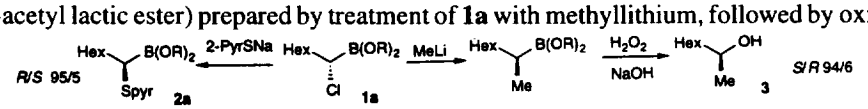
4. In a typical procedure, sodium 2-pyridylthiolate (0.55 mmol), first prepared from 2-mercaptopyridine and MeONa in MeOH (Bowman, R.; Richardson, G.D. *J. Chem. Soc. Perkin I*, **1980**, 1407), was added at rt to a solution of the (1-halogenoalkyl)boronic ester (0.5 mmol) in 5 mL of THF. The mixture was kept 12 h at rt and concentrated. The residue was dissolved in ether (20 mL) and the organic layer washed with water. Distillation of the solvent afforded an oil which was directly analysed by ^1H NMR. Yields 80–90%.
5. A 1:1 mixture of diastereoisomers **1** (R=Hex) was prepared by conducting the homologation reaction with the achiral pinacol ester followed by transesterification with (+)-pinanediol.
6. A good agreement can be seen between the diastereoisomeric purity of a (+)-pinanediol ester **2a** (R=Hex) and the enantiomeric purity of the alcohol **3** (determined by capillary gas chromatography of the O-acetyl lactic ester) prepared by treatment of **1a** with methyllithium, followed by oxidation.[1]



7. Starting (1-chloroalkyl)boronates **1** were prepared by homologation of the corresponding boronic ester,[1] execpt **2c**, **2e** and **2g**. **2c** and **2e** were directly prepared by Michael type addition of 2-mercaptopyridine to the corresponding alkene in the presence of triethylamine. In a typical procedure, a mixture of alkenyl boronic ester (1 mmol), 2-mercaptopyridine (1 mmol) and

triethylamine (1 mmol) in 10 mL of dried dichloromethane was kept at room temperature for 15 h. The solution was washed with 0.1 N HCl and brine. Concentration afforded an oil (1/1 mixture of diastereoisomers) which spontaneously crystallized (**2c**) or was chromatographied on silica gel (**2e**). **2g** was directly prepared by radical addition of the O-pivaloyl derivative of N-hydroxypyridine-2-thione to (+)-2,3-pinanediol vinylboronate. A mixture of 1/1 diastereoisomers was obtained. For experimental procedure, see: Guennouni, N.; Lhermitte, F.; Cochard, S.; Carboni, B. *Tetrahedron*, **1995**, *51*, 6999.

8. Significative non equivalences of most of signals were also observed in the ^{13}C NMR spectra.
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11. **$2a_1$** : mp=112–113°C. $[\alpha]_D^{26}$ +164.8 (c 0.99, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, δ(ppm), J(Hz)): 0.84–0.89 (m, 6H), 1.23–1.54 (m, 10H), 1.27 (s, 3H), 1.28 (s, 3H), 1.44 (d, J=10.2, 1H), 1.87–1.97 (m, 3H), 1.99 (t, J=5.6, 1H), 2.13–2.19 (m, 1H), 2.40 (ddt, J=2.2, 8.3 and 14.1, 1H), 2.46 (dd, J=3.7 and 11.2, 1H), 4.45 (dd J=1.2 and 8.2, 1H), 7.13 (dt, J=0.9 and 7.0, 1H), 7.33 (d, J=8.2, 1H), 7.69 (dt, J=1.5 and 8.5, 1H), 8.29 (d, J=5.6, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$, δ): 14.1 (CH_3), 227 (CH_2), 24.3 (CH_3), 26.9 (CH_2), 27.4 (CH_3, 29.1 (CH_2), 29.8 (CH_2), 30.2 (CH_3), 31.8 (CH_2), 33.3 (CH_2), 37.8 (C), 40.0 (CH_2), 40.1 (CH), 53.4 (CH), 78.0 (CH), 83.2 (C), 119.0 (CH), 122.8 (CH), 140.0 (CH), 141.8 (CH), 163.1 (C). ^{11}B NMR (96 MHz, $CDCl_3$, δ): 14.6. Anal. Calc. for $C_{22}H_{34}BNO_2S$ (387.2): C, 68.21; H, 8.85; N, 3.62. Found: C, 67.9; H, 8.7; N, 3.6.
12. $BC_{24}H_{30}NO_4S_2$; MW 471.45; orthorhombic, $P2_12_12_1$, a=10.187(2), b=12.585(2), c=18.846(5) Å, V=2416(1) $Å^3$, Z=4, ρ=1.296 $g.cm^{-3}$, μ=2.394 cm^{-1}, F(000)=1000, R=0.025 for 2015 observations. X-Ray crystallographic data are available from the Cambridge Crystallographic Data Centre.
13. This observation was in full agreement with the postulated mechanism in the additon of organometallic reagents to pinanediol (1-halogenoalkyl) boronate. See Ref. 1, p. 180.
14. (1*S*)-(1-Chloroalkyl)boronic esters were obtained by homologation of (+)-2,3-pinanediol derivatives[1].
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