Journal of Organometallic Chemistry, 256 (1983) 1–9
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

ARYLBORONIC ACIDS WITH INTRAMOLECULAR B–N INTERACTION: CONVENIENT SYNTHESIS THROUGH *ortho*-LITHIATION OF SUBSTITUTED BENZYLAMINES

MANFRED LAUER * and GÜNTER WULFF

Institute of Organic Chemistry II of the University of Düsseldorf, Universitätsstr. 1, D-4000 Düsseldorf (F.R.G.)

(Received May 17th, 1983)

Summary

Ortho-lithiation of *N,N*-dimethylbenzylamine and reaction with trimethylborate gave the corresponding boronic acid in good yields. The reaction was extended to the synthesis of various aromatic boron compounds with nitrogen-containing substituents in the *ortho*-position, including a chiral boroxin prepared from (*S*)-*N,N*-dimethyl-1-phenylethylamine. From *N*-methyl-benzylamine a stable boronium salt was obtained under certain conditions. The spectra of the newly synthesized compounds are discussed. Intramolecular B–N interaction is established by ^{11}B NMR spectroscopy.

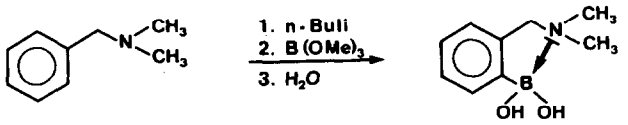
Introduction

The increasing importance of aromatic boronic acids in affinity chromatography, especially for biological or pharmaceutical purposes [1], during the past years has prompted renewed interest in convenient methods for introducing the boronic acid group or its precursors into organic molecules. Transmetallation reactions of diborane with various organometallic compounds have been studied [2], but the more usual approach is through Grignard derivatives [3]. Lithium–halogen exchange can be used, but yields tend to be lower in some cases [4]. All these methods, however, suffer from the fact that the required halogen compounds are not always easily available and have to be prepared in at least one additional step. This inconvenience can be circumvented by using direct lithiation of the unfunctionalized aromatic nucleus as described for polymeric compounds [5], where regiocontrol is of minor importance. Selective functionalization via *ortho*-lithiation, widely used in organic synthesis [6], has so far found limited application for the synthesis of aromatic boronic acids [7].

* Author to whom correspondence should be addressed.

0022-328X/83/$03.00

Because of our interest in fast and reversible interacting polymeric binding groups [8] we decided to investigate the influence of a nitrogen donor atom close to the boronic acid residue, as in **1**. This compound was first prepared in a three-step sequence starting from 2-bromotoluene [9] and its esters were reported to exhibit remarkable hydrolytic stability properties [10]. The kinetics of B–N bond breaking and formation are described in a recent article [8b]. A successful preparation of the same compound via *ortho*-lithiation was published several years ago [7a] (eq. 1), but the disappointingly low yield of 9.8% made the reported procedure unattractive from a practical point of view.



(1)

(1)

Results and discussion

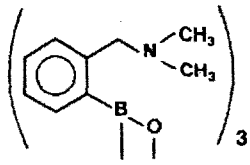
Through suitable modifications of the experimental conditions we were able to raise the yield of **1** made via *ortho*-lithiation to 60–65% (75–80% based on recovered starting material), which compares favorably with a 30% overall yield of the reported three-step procedure [7a,d]. The advantage of the regioselective boron introduction via *ortho*-lithiation was further demonstrated in the synthesis of related compounds (Table 1). To our knowledge, of the compounds in Table 1 only entry 1 has

TABLE 1

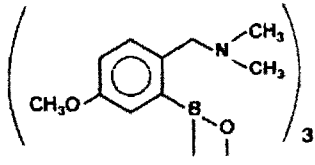
PREPARATION OF ARENE BORONIC ACIDS [a]

Entry	Compound [b]	Starting material	Lithiation conditions [c]	Isolation [d] procedure	Yield (%) [e]
1	**1**	[(dimethylamino)methyl]-benzene	TMEDA, Et_2O, 8 h, r.t.	A	60–65 (75–80)
2	**2**	4-methoxy-[(dimethylamino)methyl]benzene	Et_2O, 18 h, r.t.	B	40 (55)
3	**3**	4-dimethylamino[(dimethylamino)methyl]benzene	Et_2O, 18 h, r.t	B	37 (74)
4	**4**	2,6-bis[(dimethylamino)-methyl]benzene	TMEDA, Et_2O, 8 h, r.t.	B	5–10
5	**5**	[(methylamino)methyl]-benzene	2 eq. n-butyllithium TMEDA, Et_2O at reflux, 4 h	B	52
6	**6**	2-phenylpiperidine	2 eq. n-butyllithium TMEDA, Et_2O, 8 h, r.t.	C	27
7	**7**	1-[(dimethylamino)ethyl]-benzene	TMEDA, Et_2O at reflux, 7 h	B	40–46
8	**8**	1-[(dimethylamino)methyl]-naphthalene	TMEDA, Et_2O, 6 h, r.t.	D	20
9	**9**	dimethylaminobenzene	TMEDA, Et_2O at reflux, 2 h	E	45

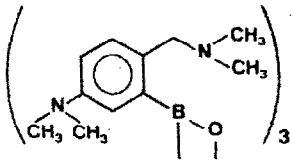
[a] For melting point, ^1H NMR and elemental analysis of the new compounds see Experimental. [b] Several compounds were isolated as the trimeric anhydrides (boroxines). [c] 1 equivalent of n-butyllithium was used unless otherwise noted. TMEDA stands for 1 equivalent of added tetramethylethylene diamine. [d] See experimental. [e] Isolated yield; yields based on recovered starting material are given in parenthesis.



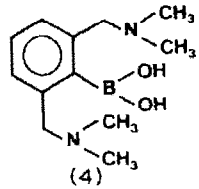
(1)



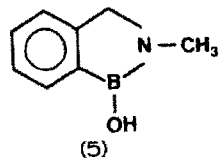
(2)



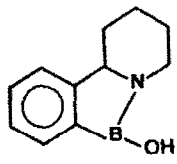
(3)



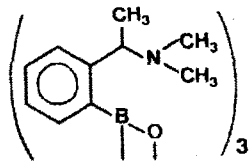
(4)



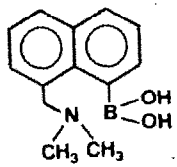
(5)



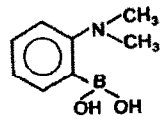
(6)



(7)



(8)



(9)

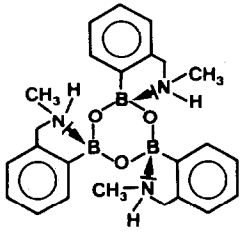
previously been reported. Although isolated yields were only moderate, typically around 40%, reaction 1 provides direct access to a variety of *ortho*-substituted, nitrogen-containing areneboronic acids starting from readily available amines [11].

Lithiation *ortho* to the strongest directing group was confirmed by ^{11}B NMR spectroscopy after conversion of the boroxines to the corresponding cyclic esters with 2,2-dimethyl-1,3-propandiol [8c]. The more soluble 1,3,2-dioxaborinanes showed absorptions between 5 and 14 ppm relative to boron trifluoride etherate, a region specific for a sp^3-coordinated boron atom with a strong B–N interaction [12]. Only the *N*,*N*-dimethylaniline derivative (entry 9) was, as expected from examination of CPK models, unable to exhibit intramolecular coordination and gave the anticipated

^{11}B shift at 27.9 ppm. The introduction of the boron atom *ortho* to the dimethylaminomethyl group (and not *ortho* to the weaker directing methoxy or dimethylamino groups [13] in entry 2 and 3 is therefore clearly indicated by ^{11}B shifts of 11.6 and 12.5 ppm, respectively, in their cyclic esters [8c].

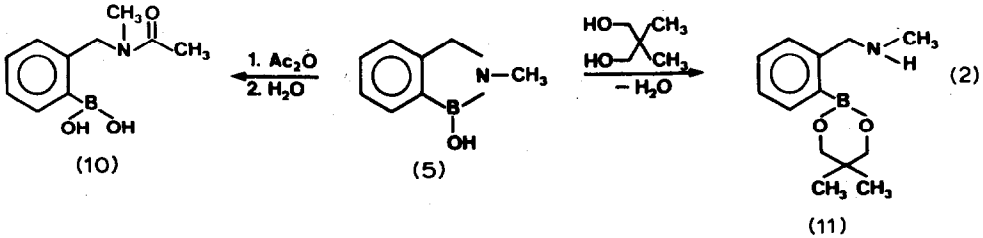
Entry 4 (Table 1) serves to illustrate the limitations of the direct lithiation. The low yields in this case can be explained in terms of preferential attack of the butyllithium reagent at one of the two peripheral positions and not at the sterically congested position between the two aminomethyl substituents. The crude product, isolated in about 50% yield, proved to be a mixture of both isomeric boronic acids as shown by ^1H NMR spectroscopy. The desired symmetrical compound could be isolated, although in poor yield, by fractional crystallization from water, but a more satisfactory synthesis would have to start from the corresponding aryl bromide to avoid the regioselectivity problems [14]. Steric hindrance is probably also responsible for the resistance of compound **4** towards dehydration to the corresponding boroxine, as postulated for similar compounds [7c,9].

When boron derivatives derived from secondary amines were dehydrated in toluene, the product could be either the monomeric **5** or the trimeric **5a** [15].



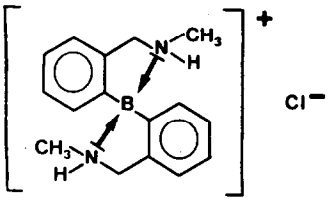
(5a)

Since elemental analysis and ^1H NMR spectroscopy are of little help in distinguishing between the two isomers, we assigned structure **5** on the basis of the mass spectrum. This had the base peak at *m/e* 147, and a smaller peak at *m/e* 276 (corresponding to the dimeric anhydride structure) which probably arose from dehydration in the ion source [16], but no trace of the trimer **5a** could be detected. Assignment of monomeric structure **5** was confirmed by molecular weight determinations by vapour pressure osmometry in chloroform (Found 144; calcd. 147). Unfortunately, the solubility of **6** was too low for similar osmometric studies, but the mass spectrum again agreed with the monomeric structure **6** depicted in Table 1 (found: *m/e* 187 and 356, corresponding to monomer and dimer, respectively). In any case B–N bond formation must be clearly reversible, since reaction of **5** or **6** with 2,2-dimethyl-1,3-propandiol gave the corresponding 1,3,2-dioxaborinanes without difficulty [8c]. Similarly, acetylation of **5** with acetic anhydride proceeded smoothly to give the boronic acid **10** in good yields (eq. 2).



(10) (5) (11) (2)

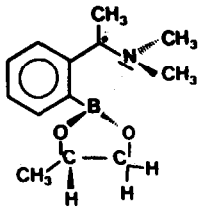
Compound **5** was purified by distillation of the corresponding methyl ester and subsequent hydrolysis (procedure B). When we tried to take advantage of the poor solubility in ethyl acetate to use the simpler work up procedure A, however, a white solid precipitated gradually from ethyl acetate in yields up to 25% but this was not the expected 1,3-dihydro-1-hydroxy-2-methyl-2,1-benzazaborol (**5**). It was soluble in both water and chloroform without decomposition, and appeared to be very stable at room temperature. The simplicity of its ^1H NMR spectrum in deuterochloroform, showing an AB pattern for the methylene protons, was intriguing in comparison with the quite complicated spectra obtained in more polar solvents. We finally assigned structure **12** on the basis of NMR data (^1H (in $CDCl_3$): δ 2.47 ppm (s, 6H, 2 CH_3), 3.92 (d, J 15 Hz, 2H, CH_2), 5.25 (d, J 15 Hz, 2H, CH_2), 7.1–7.4 (m, 8H, aromatic), 8.76 (br. s, 2 H, NH, may be coupled with methyl and methylene protons, and can be exchanged with D_2O); ^{13}C (in $CDCl_3$): 38.5, 59.6, 122.7, 127.3, 128.6, 131.5, 141.5 ppm; ^{11}B (in $CHCl_3$, vs. BF_3/Et_2O): 10.1 ppm); mass spectra (base peak at m/e 251 corresponding to the boronium moiety) and elemental analysis (Calcd. (found) for $C_{16}H_{20}BClN$ (in %) C, 67.04 (67.37); H, 7.05 (7.04); B, 3.77 (3.55; Cl, 12.37 (12.1); N, 9.78 (9.67)).



(12)

Compound **12**, made from reaction of two lithiated aryl groups with one molecule of trimethyl borate, is formally a diaryl borane stabilized as a boronium ion through intramolecular coordination with two nitrogen donors [17]. The presence of the chloride anion can be accounted for in terms of reaction with the dichloromethane used for extraction, as reported for similar systems [18]. The simplicity of the NMR spectra in chloroform at room temperature and down to $-60°C$ implies a symmetrical structure, as depicted in **12**, or a compound with two different nitrogen atoms which are rapidly exchanging on the NMR time scale. Either the structure or the rate of equilibration is highly solvent-dependent, because for a solution of **12** in dimethyl sulfoxide a temperature above 160°C is required before the spectral features are similar to those obtained in chloroform at room temperature.

When boroxine **7** was prepared starting from racemic *N,N*-dimethyl-1-phenylethylamine, our initial efforts to eliminate a shoulder (2.35 vs. 2.33 ppm) at the $(CH_3)_2N$ peak in the ^1H NMR spectrum, assumed to be an impurity, by repeated crystallization proved fruitless. No impurities could be detected by elemental analysis, TLC, mass spectra or conversion to cyclic esters, so we postulated a mixture of two diastereomeric boroxines arising from the chiral center at the tertiary carbon atom. Assuming random cyclization statistics, the minor component was likely to correspond to a boroxine with all chiral centers of the same configuration (i.e. *RRR* or *SSS*), and the major component to consist of all possible permutations of "mixed" chirality (i.e. *RSS*, *SRS*, etc.). The hypothesis was confirmed through synthesis of the optically pure boroxine from (*S*)-(−)-*N,N*-dimethyl-1-phenylethylamine.



(13)

The direct lithiation method thus provides access to both antipodes of boroxin **7** from commercially available enantiomers. The optical purity was shown to be higher than 95%, as verified by transformation of **7** into the ester **13** by reaction with (*S*)-1,2-propandiol [19] and ^{1}H NMR investigation in deuterobenzene. Under these conditions the methyl signals of the α-CH_3 group and of the diol-CH_3 group of the [(*S*), (*S*)] and the [(*R*),(*S*)] compound [20] were clearly distinguishable (δ 1.32 (1.35) (d, *J* 6 Hz, α-CH_3), 0.90 (0.92) (d, *J* 7 Hz), diol-CH_3)).

Unfortunately, the initial objective of assigning the absolute stereochemistry of a diol by reaction with (*S*)-**7** and following NMR spectroscopy [21] could not be achieved because of the relatively small differences in chemical shifts in the ^{13}C spectrum (δ 12.67 (12.81); 21.50 (21.69) ppm). The differences between [(*R*),(*S*)]-**13** and [(*S*),(*S*)]-**13** were also too small to give satisfactory GC separation on an achiral stationary phase [22]. The two diastereomers can be separated on a chiral phase [23].

Experimental

General procedure [24]

In a typical experiment 160 ml (0.26 *M*) of a 1.6 *N* n-butyllithium solution (in hexane) were added to a solution of 33.8 g (0.25 *M*) *N*,*N*-dimethylbenzylamine and 29 g (0.25 *M*) tetramethylethylenediamine (TMEDA) in 300 ml ether and stirred for 8 h at room temperature. The resulting suspension was precooled and siphoned into a vigorously stirred reaction vessel cooled in a methanol/dry ice bath with simultaneous addition of a solution of 40 ml (0.35 *M*) trimethylborate in 50 ml of ether. The addition, which typically took less than half an hour, was carried out as rapidly as possible consistent with keeping the temperature below −60°C. The resulting mixture was allowed to warm up to room temperature during 24 h and worked up by one of the methods A–E below.

(A) Evaporation to dryness and suspension of the remaining residue in dichloromethane separated the soluble dimethyl-ester from insoluble material. The combined filtrates were subsequently treated with water and then evaporated to dryness. Azeotropic water removal in refluxing toluene and recrystallization from toluene gave the desired boroxin. The starting amine could be recovered from the mother solution.

(B) The dichloromethane extract obtained according to procedure A was not immediately hydrolyzed but distilled under reduced pressure. The crude boronic acid dimethyl ester [25] thus separated from starting material was then hydrolyzed to give the desired compound after azeotropic water removal and recrystallization from toluene or dichloromethane/petrol ether.

(C) The crude reaction product was extracted several times with water. The aqueous phase was neutralized with HCl and evaporated to dryness. Water removal

and continuous extraction with hot toluene, followed by solvent evaporation and treatment of the remaining oil with methanol yielded the pure, crystalline dimethyl ester, which was hydrolyzed as usual.

(D) Unreacted starting material was removed from the dichloromethane extract in vacuo and the residue purified by chromatography on alumina. The dimethyl-ester was readily hydrolyzed to the boronic acid.

(E) After hydrolysis and removal of the organic layer at pH 11 the remaining solution was adjusted to pH 8 and extracted repeatedly with chloroform. The organic layer was dried and concentrated, and the product was recrystallized from hexane.

2-(N-Acetyl-N-methyl-aminomethyl)-phenyl boronic acid (10)

This compound was obtained in 87% yield through reaction of equivalent amounts of **5** and acetic anhydride in CH_2Cl_2 for 16 h, recrystallized from water and air-dried.

Analytical data for newly synthesized boronic acids (boroxins) were as follows:

m. p. (b. p. of the methylester/mmHg pressure); sum formula; C, H, N calcd. (found), ^1H NMR ($CDCl_3$): δ in ppm, J in Hz.

2: 185°C (120–130°C/0.2 mmHg); $C_{30}H_{42}B_3N_3O_6$; 62.87; 7.39, 7.33 (63.17, 7.39, 7.24); δ 2.40 (s, 6H), 3.78 (s, 3 + 2H), 6.73–7.13 (m, 3H).

3: 181°C (142°C/1 mmHg); $C_{33}H_{51}B_3N_6O_3$; 64.74, 8.40, 13.73, (64.97, 8.41, 13.49). δ 2.42 (s, 6H), 2.88 (s, 6H), 3.76 (s, 2H), 6.5–7.2 (m, 3H).

4: 131–133°C (105–110°C/0.05 mmHg); $C_{12}H_{21}BN_2O_2$; 61.04, 8.97, 11.86, (60.82, 9.09, 12.08); δ 2.33 (s, 12H), 3.67 (s, 4H), 5.35 (broad, 2H), 6.9–7.3 (m, 3H).

5: 194–195°C (70–80°C/0.5 mmHg); $C_8H_{10}BNO$; 65.38; 6.86, 9.53 (65.11, 6.81, 9.23); δ 2.11 (s, 3H), 3.49 (br., 1H) 7.0–7.8 (m, 4H).

6: 204–205°C, ——; $C_{11}H_{14}BNO$; 70.62, 7.56, 7.49 (70.49, 7.80, 7.19); δ (MeOH-d_4) 1.5–2.6 (m, 6H), 2.7–3.1 (m, 2H), 3.8–4.2 (m, 1H), 4.65 (br., 1H), 7.05–7.35 (m, 4H).

(*R*),(*S*)-**7**: 179–180°C (95–105°C/0.2 mmHg); $C_{30}H_{42}B_3N_3O_3$; 68.62, 8.06, 8.00 (68.40, 8.00, 7.83); δ 1.34 (d, J 7, 3H), 2.29 + 2.31 (2s [3/1], 6H), 4.22(m, 1H), 7.1–7.8 (m, 4H).

(*S*)-**7**: 116–117°C (95–105°/0.2); $C_{30}H_{42}B_3N_3O_3$; 68.62, 8.06, 8.00, (68.45, 8.09, 7.89); δ 1.34 (d, J 7, 3H), 2.31 (s, 6H), 4.22 (q, J 7, 1H), 7.1–7.8 (m, 4H).

8: 159–160°C (m.p. 95–96°C); $C_{13}H_{16}BNO_2$; 68.16, 7.04, 6.11, (67.41, 6.95, 5.84); δ 1.72 (s, 2H), 2.53 (s, 6H), 4.27 (s, 2H), 7.1–7.9 (m, 6H).

9: 79°C, ——; $C_8H_{12}BNO_2$; 58.24, 7.33, 8.49, (57.84, 7.00, 8.03); δ 2.70 (s, 6H), 7.13–7.53 (m, 3H), 7.87–8.00 (m, 1H).

10: 132–135°C, ——; $C_{10}H_{14}BNO_3$; 58.00, 6.83, 6.77 (58.11, 6.96, 6.73); δ (DMSO-d_6 at 75°C) 2.03 (s, 3H), 2.88 (s, 3H), 4.67 (s, 2H), 6.95–7.65 (m, 4H) 5–7 (br., 2H).

Acknowledgement

Thanks are due to Fonds der Chemischen Industrie and the "Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen for financial support. We also express appreciation of the assistance of H. Böhnke, I. Karnuth and M. Salehnia, who performed some of the experiments.

References

1 W. Kliegel: Bor in Biologie, Medizin und Pharmazie, Springer Verlag, Heidelberg 1980; M. Glad, S. Ohlson, L. Hansson, M. Mansson and K. Mosbach, J. Chromatogr., 200 (1980) 254; Amicon Corp.: Boronate Ligands in Biochemical Separations, Amicon Corp., Danvers 1981.

2 H. Iida, H. Kitamura, K. Seita and K. Yamada, Bull. Chem. Soc. Jpn., 47 (1974) 1028; F.G. Thorpe, G.M. Pickles and J.C. Podesta; J. Organomet. Chem., 128 (1977) 305; F.G. Thorpe, S.W. Breuer, G.M. Pickles, T. Spencer and J.C. Podesta, J. Organomet. Chem., 145 (1978) C26; N.P. Bullen, P. Hodge and F.G. Thorpe, J. Chem. Soc., Perkin Trans. I, (1981) 1863; G.M. Pickles, T. Spencer, F.G. Thorpe, A.D. Ayala and J.C. Podesta, J. Chem. Soc., Perkin Trans. I., (1982) 2949.

3 R.M. Washburn, E. Levens, C.F. Albright, F.A. Billig and E.S. Cernak, Adv. Chem. Series, 23 (1959) 102; R.M. Washburn, F.A. Billig, H. Bloom, C.F. Albright and E. Levens, Adv. Chem. Ser. 32 (1961) 208; Organic Syntheses, Coll. Vol. 4, 68; H.A. Staab and B. Meissner; Liebigs Ann. Chem., 753 (1971) 80;

4 R.L. Letsinger and S.H. Dandegaonker, J. Am. Chem. Soc., 81 (1959) 498; D.R. Nielsen and W.E. McEwen, J. Am. Chem. Soc., 79 (1957) 3081; I.G.C. Coutts, H.R. Goldschmid and O.C. Musgrave, J. Chem. Soc. (C), (1970) 488.

5 M.J. Farall and J.M. Frechet, J. Org. Chem., 41 (1976) 3877; M. Hartmann and H. Carlson, Makromol. Chem., 178 (1977) 383.

6 (a) H.W. Gschwend and H.R. Rodriguez, Org. Reactions, 26 (1979) 1; (b) P. Beak and V. Snieckus, Acc. Chem. Res., 15 (1982) 306.

7 (a) R.T. Hawkins and D.B. Stroup, J. Org. Chem., 34 (1969) 1173; (b) G. Marr, R.E. Moore and B.W. Rockett, J. Organomet. Chem., 7 (1967) P11; (c) D.Q. Quan, Bull. Soc. Chim. (France), (1973) 767; (d) R. Grotstollen, dissertation, Düsseldorf 1981.

8 (a) G. Wulff, Pure Appl. Chem., 54 (1982) 2093; (b) T. Burgemeister, R. Grobe-Einsler, R. Grotstollen, A. Mannschreck and G. Wulff, Chem Ber., 114 (1981) 3403; (c) M. Lauer, H. Böhnke, R. Grotstollen, M. Salehnia and G. Wulff, Chem. Ber., in preparation.

9 R.T. Hawkins and H.R. Snyder, J. Am. Chem. Soc., 82 (1960) 3053 and 3863.

10 R. Clement and M. Francois, Compt. Rend. Acad. Sci. Paris, (1967) 923 and 977.

11 If these were not commercially available they were prepared by the Eschweiler-Clarke procedure (M.L. Moore in Org. Reactions 5, (1957) 323) or according to the following references: 2-Phenylpiperidine: C.G. Overberger and L.P. Herin, J. Org. Chem. 27 (1962) 417; *N,N*-Dimethylnaphthylamine: R.L. Gay and C.R. Hauser, J. Am. Chem. Soc., 89 (1967) 2297.

12 H. Nöth and B. Wrackmeyer, NMR Basic principles and Progress, Vol. 14, Nuclear Magnetic Resonance Spectroscopy of Boron Compounds; Springer Verlag, Berlin 1978.

13 D.W. Slocum and C.A. Jennings, J. Org. Chem., 41 (1976) 3653.

14 D.M. Grove, G. van Koten, J.N. Louwen, J.G. Noltes, A.L. Spek, and M.J.C. Ubbels, J. Am. Chem. Soc., 104 (1982) 6609.

15 For homologues of **5** see: (a) R. Köster and K. Iwasaki, Adv. Chem. Ser., 42 (1964) 148; (b) R.T. Hawkins and A.U. Blackham, J. Org. Chem., 32 (1967) 597; (c) H.E. Dunn, J.C. Catlin and H.R. Snyder, J. Org. Chem, 33 (1968) 4483.

16 The boronaphthalide system can dehydrate to the dimer upon sublimation in vacuo; see ref. 15(b).

17 For discussions of boronium ions see references cited by J.D. Odom in G. Wilkinson, F.A. Stone, E.W. Abel (Eds.), Comprehensive Organometallic Chemistry Vol. 1, 253–310, Pergamon Press, Oxford 1982.

18 A.M. Cowley and J.L. Mills, J. Am. Chem. Soc., 91 (1969) 2911; U. Gerwarth, Z. Naturforsch. B, 32 (1979) 1084.

19 L.H. Klemm, W. Stalick and D. Bradway, Tetrahedron 20, (1969) 1667; C. Malanga, N. Spassky, R. Menicagli and E. Chiellini, Synth. Comm. 12 (1982) 67.

20 The first letter denotes the configuration of the boronic acid, the second the configuration of the diol. NMR data of the [(*R*)-(*S*)] compound are given in parentheses.

21 For the use of boronic acids as aids in stereochemical assignments see M.C. García-Alvarez, B. Rodríguez, A. García-Granados and A.S. de Buruaga, J. Org. Chem. 47 (1982) 3571 and references cited therein.

22 50 m capillary column OV 17 at 170°C.

23 We thank J. Vietmeier for performing these measurements, which were on a 25 m capillary "Chirasil Val" column (Applied Science, USA) at 170°C.
24 For general lithiation conditions see the references cited in review article [6].
25 In the case of derivative **5**, ring closure and loss of methanol occur upon distillation to give the cyclic monomethyl ester.