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Chiral synthesis via organoboranes

XVI. Boroxazolidones derived from α-amino acids and borinic or boronic esters. A simple procedure for upgrading borinates and boronates to materials of high optical purity *

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Abstract

The synthesis of boron heterocycles from borinic and boronic esters with α-amino acids was explored as a means of upgrading the optical purities of intermediates from asymmetric hydroboration. *B*-Methoxy-9-borabicyclo[3.3.1]nonane, methyl dicyclohexylborinate and (+)- and (−)-methyl diisopinocampheylborinate react with various α-amino acids to form the corresponding crystalline chelates. Recrystallization of the chelates derived from methyl *trans*-2-phenylcyclopentylisopinocampheylborinate of 85% ee with *l*-phenylalanine, methyl isopinocampheyl-*exo*-norbornylborinate of 83% ee with *l*-proline and both optical isomers of methyl diisopinocampheylborinate of 92% ee with *l*-proline yield the corresponding products with optical purities approaching 100% ee. Dimethyl cyclopentylboronate, dimethyl *exo*-norbornylboronate and dimethyl isopinocampheylboronate upon treatment with iminodiacetic acid and *N*-methyliminodiacetic acid form the corresponding bicyclic boronates. Recrystallization of the chelate derived from diethyl 3-tetrahydropyranylboronate and iminodiacetic acid yields a product of essentially 100% ee. Consequently formation of boroxazolidones of asymmetric hydroboration products provides one possible route to upgrade such products to materials of high optical purity.

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* Dedicated to Prof. Colin Eaborn in recognition of his important contributions to organometallic chemistry.

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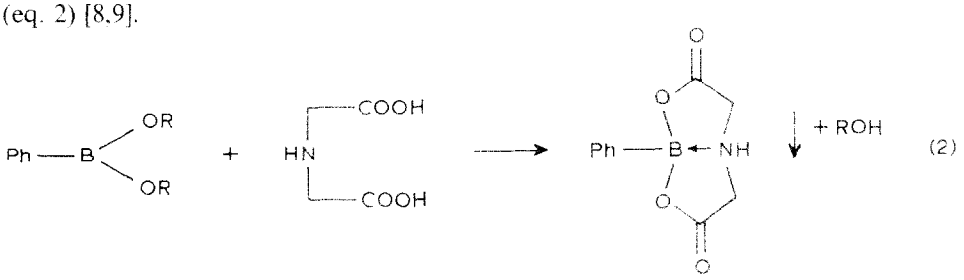
Introduction

Amino alcohol-borinate derivatives with intramolecular N–B coordination have been widely used to precipitate borinates from reaction mixtures [1–3]. Borinates are also known to form chelate compounds with α-amino acids, boroxazolidones [4–6]. Recently borinic and boronic acids have been utilized for the secretion of α-amino acids from living cells [5,6]. Our current interest [7] in this area prompted us to look into compounds of this type as a possible means of upgrading borinates or boronates of less than 100% ee to materials approaching 100% ee. Reaction of α-amino acids with various borinic acids, such as diphenylborinic acid or 9-borabicyclo[3.3.1]nonylborinate leads to formation of stable adducts in which the α-amino and the carboxyl groups are bound to boron, forming chelate derivatives [4]. A typical example is shown in eq. 1.

(1)

Similarly the reaction of phenylboronic acid or dimethyl thexylboronate with iminodiacetic acid leads to the formation of air stable bicyclic chelate compounds (eq. 2) [8,9].

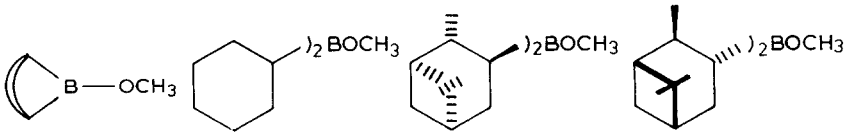


(2)

Since these crystalline chelates are stable in the air, they can be used to store the borinates and boronates. Recently this laboratory reported that crystalline chelates, derived from borinates and boronates with various aminoalcohols, provide a satisfactory route to achieve the upgrading of the optical purity of the R^*–B moiety [7]. Masamune and coworkers [10] recently used this strategy first to isolate the *cis*- and *trans*-isomers of *B*-methoxy-2,5-dimethylborinanes and then to resolve the two enantiomers of *B*-methoxy-*trans*-2,5-dimethylborinane. In this paper we report the reaction of borinates and boronates with α-amino acids and the application of this study to achieve the upgrading of the *trans*-2-phenylcyclopentyl, diisopinocampheyl, *exo*-norbornyl and the 3-tetrahydropyranyl derivatives from 83–92% ee to materials approaching 100% ee.

Results and discussion

Representative borinates and boronates of different steric requirement were selected for an exploratory study. The borinates selected were *B*-methoxy-9-borabicyclo[3.3.1]nonane (**1**), methyl dicyclohexylborinate (**2**), and methyl (+)- and (−)-diisopinocampheylborinates (**3**).

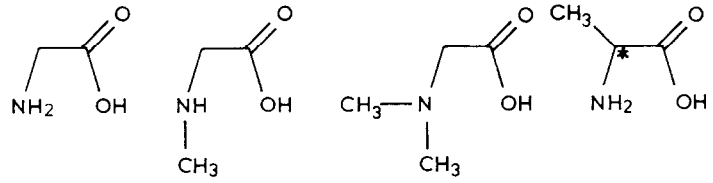


(1) (2) ((+)-3) ((−)-3)

From (−)-α-pinene From (+)-α-pinene

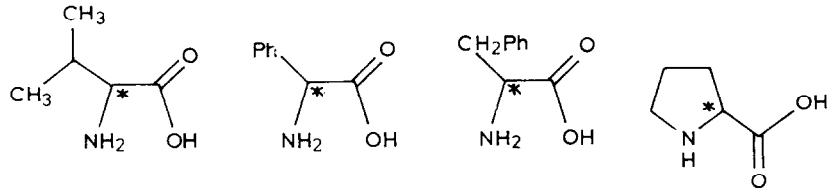
These borinates were prepared by methanolysis of the corresponding dialkylboranes.

Reaction of borinates with α-amino acids. Borinates **1**, **2**, and (+)-**3** and (−)-**3** react with glycine **4** to give white crystalline compounds. The formation of the B←N bond in the ester (chelation) was confirmed by an upfield shift in the ^{11}B NMR signal from around δ +52 to +6–14 ppm. Similarly borinate **1** formed chelates with *N*-methylglycine (**5**) and *N*,*N*-dimethylglycine (**6**). However, borinates **2**, and (+)-**3** and (−)-**3** give a viscous liquid with **5** and **6**, transesterification products, with no chelation, as indicated by the ^{11}B NMR signals at ~ δ 52 ppm. This establishes that as the steric bulk around the boron increases, the more bulky *N*-substituted glycines resist chelation. But substitution on the α-carbon of the glycine structure does not reveal any interference with the formation of the chelate B–N bond for these three borinates.



(4) (5) (6) (7)

Other α-amino acids such as alanine (**7**), valine (**8**), phenylglycine (**9**), phenylalanine (**10**) also form white crystalline solid derivatives with these borinates.



(8) (9) (10) (11)

However *l*-proline (**11**) forms a chelate only with the (+)-borinate (**3**) derived from (−)-α-pinene, as indicated by the ^{11}B NMR signal at δ +7.2 ppm. On the other hand, the (−)-borinate (**3**), derived from (+)-α-pinene, on treatment with *l*-proline gives only a viscous liquid without chelation (^{11}B NMR signal at δ +54.2 ppm). These results are summarized in Table 1.

Reaction of boronates with iminodiacetic acids. The three representative boronates, dimethyl cyclopentylboronate, dimethyl *exo*-norbornylboronate and dimethyl isopinocampheylboronate were prepared from the corresponding olefins via hydro-

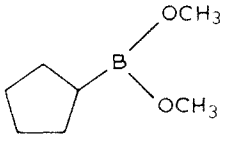
Table 1

Physical and ^{11}B NMR data of chelates derived from the test borinates and representative amino acids

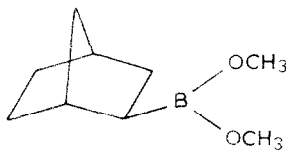
Borinate	Amino acid	Yield (%)	m.p. (°C)	^{11}B NMR δ (ppm)
1	**4**	95	226–228	+11.6
2	**4**	96	228–230	+8.2
(−)-**3** [a]	**4**	92	223–224	+6.7
(+)-**3** [b]	**4**	90	230–232(d)	+7.2
1	**5**	94	278–280	+17.9
2	**5**	95		+54.3
(−)-**3**	**5**	96		+51.1
(+)-**3**	**5**	92		+52.0
1	**6**	92	210–212	+11.7
2	**6**	95		+52.3
(−)-**3**	**6**	94		+53.0
(+)-**3**	**6**	95		+54.0
1	**7**	90	228–290	+7.6
2	**7**	92	218–220(d)	+8.6
(−)-**3**	**7**	94	295–296	+7.3
(+)-**3**	**7**	92	285–286	+8.2
1	**8**	85	219–220	+12.4
2	**8**	91	264–266	+9.9
(−)-**3**	**8**	90	178–180	+7.0
(+)-**3**	**8**	92	180–182	+6.8
1	**9**	85	176–178	+8.5
2	**9**	90	188–190	+6.7
(−)-**3**	**9**	89	201–202	+9.4
(+)-**3**	**9**	87	197–198	+7.0
1	**10**	95	178–180	+7.5
2	**10**	96	196–197	+5.3
(−)-**3**	**10**	86	188–189	+6.5
(+)-**3**	**10**	90	206–207	+7.2
1	(*S*)-(−)-**11**	87	264–265	+8.2
2	(*S*)-(−)-**11**	92	248–250	+7.0
(−)-**3**	(*S*)-(−)-**11**	88		+54.2
(+)-**3**	(*S*)-(−)-**11**	90	178–180	+7.2

[a] Derived from (+)-α-pinene, > 99% ee. [b] Derived from (−)-α-pinene > 99% ee.

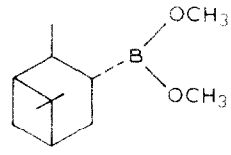
boration with dibromoborane-methyl sulfide followed by hydrolysis and esterification with methanol [11]. Treatment of these boronates, **12**–**14**, with either imino-



(**12**)



(**13**)



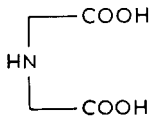
(**14**)

diacetic acid (**15**) or *N*-methyliminodiacetic acid (**16**), results in the formation of crystalline chelates, the ^{11}B NMR clearly revealing the formation of B←N bonds. The results are summarized in Table 2.

Table 2

Physical and ^{11}B NMR data of chelates derived from the test boronates and iminodiacetic acids

Boronate	Iminodiacetic acid	Yield (%)	m.p. (°C)	^{11}B NMR (DMSO)
12	**15**	88	230–231	+12.9
13	**15**	89	234–235	+12.7
14	**15**	92	232(d)	+12.6
12	**16**	90	235–240	+13.1
13	**16**	87	254–255(d)	+12.4
14	**16**	91	256–260	+12.9



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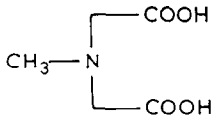
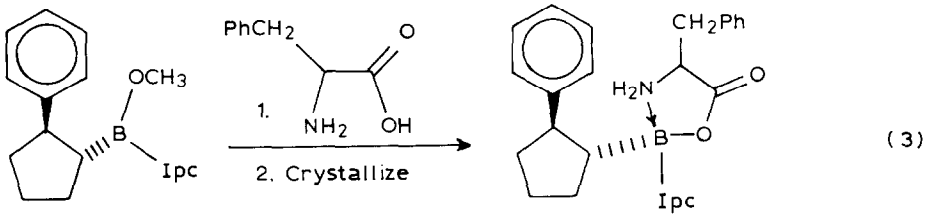


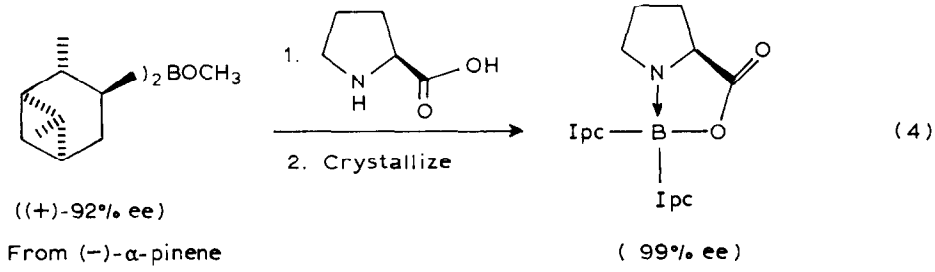
(16)

Upgrading the optical purity of borinates and boronates. Hydroboration of 1-phenylcyclopentene with (−)-IpcBH$_2$ at −25°C followed by methanolysis produces methyl *trans*-2-phenylcyclopentylisopinocampheylborinate of 85% ee. Treatment of the borinate with *l*-phenylalanine in aqueous ethanol gave a crystalline chelate (^{11}B NMR signal at δ +6.4 ppm). The chelate was crystallized from DMSO at 0°C. The crystalline chelate thus obtained was treated with dilute hydrochloric acid, followed by acetaldehyde, and then oxidized by alkaline hydrogen peroxide to give *trans*-2-phenylcyclopentanol of > 99% ee (eq. 3): $[\alpha]_D^{23}$ +83.54° (*c* 1.5, EtOH) (Lit. [12] $[\alpha]_D^{23}$ +83.6° (*c* 1.5, EtOH)).



(85% ee) (>99% ee) (3)

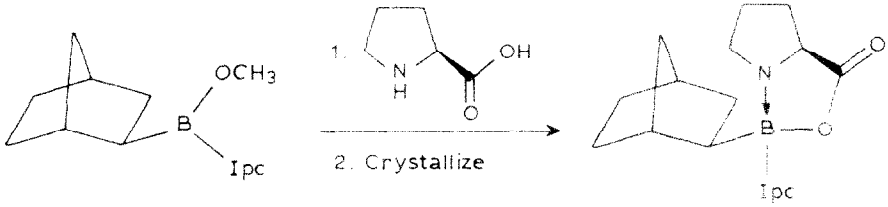
Similarly methyl diisopinocampheylborinate of 92% ee ((+)-**3**) was treated with *l*-proline to give a crystalline chelate, recrystallized from methanol, to give the boroxazolidone. Treatment with dilute hydrochloric acid, followed by oxidation, gave (+)-isopinocampheol of > 99% ee (eq. 4). Hydroboration of norbornene with



((+)-92% ee) (99% ee) (4)

From (−)-α-pinene

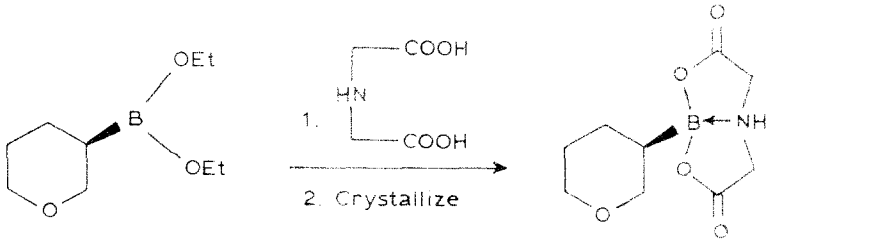
(+)-diisopinocampheylborane produces *exo*-norbornyldiisopinocampheylborane of 83% ee. The trialkylborane, upon treatment with water, followed by acetaldehyde, eliminates one α-pinene group cleanly. Treatment of the borinate derived from (−)-α-pinene with *l*-proline forms the chelate. This chelate could be crystallized from a 3/1 methanol/pentane mixture. Following a single recrystallization, the crystalline chelate thus obtained was treated with dilute hydrochloric acid followed by acetaldehyde and then oxidized to give *exo*-norborneol $[\alpha]_D^{23}$ +5.2° (*c* 7.5, EtOH) (Lit. [7] $[\alpha]_D^{23}$ +5.17° (*c* 7.5, EtOH)] in essentially 100% ee (eq. 5).



(5)

(83% ee) (>99%)

Hydroboration-oxidation of 3,4-dihydropyran with diisopinocampheylborane from (+)-α-pinene yields (+)-3-hydroxytetrahydropyran in 83% ee. Treatment of the 3-tetrahydropyranyldiisopinocampheylborane with acetaldehyde provides the diethyl boronate. Iminodiacetic acid converts this boronate into a crystalline chelate. Two recrystallizations from DMSO upgrade the adduct to >99% ee. Treatment of the crystalline adduct with dilute hydrochloric acid, followed by oxidation, gives (+)-3-hydroxytetrahydropyran of >99% ee.



(6)

(83% ee) (>99%)

Conclusion

This study demonstrates the utility of chelates derived from borinic and boronic acids with selected amino acids to achieve excellent upgrading of the optical purities of the original borinates and boronates.

Experimental

The reaction flask and other glass equipment were stored in an oven at 150 °C overnight and assembled in a stream of dry nitrogen gas. Syringes were assembled and fitted with needles while hot and cooled in a stream of dry nitrogen gas. Special

experimental techniques used in handling air-sensitive materials are described in detail elsewhere [14].

Spectra. ^{11}B NMR spectra were recorded on a Varian FT-80A instrument. The chemical shifts are δ values relative to $BF_3 \cdot OEt_2$. ^1H NMR (60 MHz) were recorded on a varian T-60. IR and mass spectra were recorded on Perkin–Elmer 137 and Finnegan GC/mass spectrometers, respectively. Optical rotations were measured on a Rudolph polarimeter Autopol III.

GC analysis. All GC analyses were carried out with a Hewlett Packard 5750 chromatograph using either a (a) 12 ft $\times$ 0.125 in column packed with 10% Carbowax 20M on Chromosorb W (100–120 mesh) or a (b) 12 ft $\times$ 0.125 in column packed with 10% SE-30 on Chromosorb W (100–120 mesh). For preparative GC, either a (c) 6 ft $\times$ 0.5 in column packed with 20% Carbowax 20M on Chromosorb W (60–80 mesh) or a (d) 6 ft $\times$ 0.5 in column packed with 20% SP-2100 Chromosorb W (60–80 mesh) were used.

Materials. Borane-methyl sulfide (BMS), 9-borabicyclo[3.3.1]nonane and dibromoborane purchased from the Aldrich Chemical Company were estimated according to the standard procedure [14]. Dicyclohexylborane [15] and diisopinocampheylborane [16] were prepared according to the literature procedures. Dimethyl cyclopentylboronate, dimethyl *exo*-norbornylboronate and dimethyl isopinocampheylboronate were prepared according to the literature procedures [11]. All amino acids mentioned in this study were purchased from the Aldrich Chemical Company.

General procedure for the preparation of boroxazolidones from borinates and α-amino acids. In a 25 ml round bottom flask equipped with a septum inlet and magnetic stirring bar and connecting tube leading to a mercury bubbler was placed 2 mmol of α-amino acid in 10–15 ml of ethanol/H_2O (1/1) or DMSO (10–15 ml). To it 2 mmol of borinate (1 *M* solution in THF) was added dropwise and the reaction mixture stirred at 80–100 °C until the amino acid dissolved. After completing the reaction (^{11}B NMR), all of the solvent was removed under vacuum (1–2.0 mm) and the residue treated with methanol. The product was collected by filtration and washed with either hexane or ether.

General procedure for the preparation of chelate boronates. In the usual experiment setup was placed 2 mmol of iminodiacetic acid in DMSO (10–15 ml). To it was added 2 mmol of boronate (1 *M* solution in THF) and the reaction mixture was stirred for 2 h at 80–100 °C. After completing the reaction (^{11}B NMR), the solvent was removed under vacuum (1–2.0 mm) and the residue was treated with methanol. The solid thus obtained was filtered and washed with 5 ml of ether.

Upgrading the optical purity of methyl trans-2-phenylcyclopentylisopinocampheylborinate via l-phenylalanine. To the *l*-phenylalanine (3.3 g, 20 mmol) in 100 ml of aqueous ethanol (1/1) was added borinate from the hydroboration of 1-phenylcyclopentene with monoisopinocampheylborane (7.1 g, 22 mmol in 15 ml of THF) and the reaction mixture was stirred 80–100 °C for 2–3 h. After completing the reaction (^{11}B NMR, δ +6.4 ppm), all the solvents were evaporated in vacuo and washed with ether to remove the small excess of borinic acid. The boroxazolidones obtained were recrystallized in 25 ml of DMSO at 0 °C. The crystals obtained were freed from solvents and washed with 2 $\times$ 5 ml of methanol. The solid was dried under vacuum to give 5.9 g of the product (65% yield, m.p. 159–160 °C, ^{11}B NMR signal at δ +6.4 ppm). The chelate (5.5 g, 12 mmol) was placed in THF (50 ml) and

treated with 10 ml of 3 *M* hydrochloric acid. The reaction mixture was stirred at 25°C for 2 h. The THF layer was separated, dried over anhydrous $MgSO_4$. To it 1.7 ml (30 mmol) of chilled acetaldehyde was added with a syringe and the reaction mixture was stirred overnight. The excess acetaldehyde was pumped off and the residue was distilled to give diethyl *trans*-2-phenylcyclopentylboronate: b.p. 80–82°C/0.01 mmHg, $[\alpha]_D^{25}$ +43.2° (*c* 2.5, EtOH) (Lit. [12] $[\alpha]_D^{25}$ +43.25° (*c* 2.46, EtOH)). The boronate (5 mmol) was oxidized with 3 *M* sodium hydroxide and 30% hydrogen peroxide in the usual manner. The alcohol was extracted with ether. The product was purified by preparative GC to afford the GC pure material: b.p. 73–75°C/0.5 mmHg $[\alpha]_D^{23}$ +83.1° (*c* 1.5, EtOH) (Lit. [12] $[\alpha]_D^{23}$ +83.06° (*c* 1.565, EtOH)) > 99% ee by capillary GC of its Mosher ester.

Upgrading the optical purity of methyl diisopinocampheylborinate via l-proline. To the *l*-proline (2.3 g, 20 mmol) in methanol (25 ml) was added methyl diisopinocampheylborinate (derived from (−)-α-pinene) of 92% ee (22 mmol, 1 *M* sol in THF). The reaction mixture was stirred at 60–65°C for 0.5 h. After completion of the reaction (^{11}B NMR), the solvent was evaporated under vacuum and the residue was washed with ether to remove the slight excess of the borinic ester. The solid thus obtained was crystallized from 3/1 methanol/pentane to give upgraded adduct 5.3 g, yield 66%, m.p. 178–180°C, ^{11}B NMR δ +7.2 ppm. The chelate, 5.2 g (13.0 mmol), was placed in THF (50 ml) and treated with 10 ml of 3 *M* hydrochloric acid. The reaction mixture was stirred at 25°C for 1 h and the organic layer was separated, washed with water and dried on anhydrous $MgSO_4$. The borinic acid was re-esterified with methanol to reform the methyl diisopinocampheylboronate. The boronate, upon oxidation, gave isopinocampheol, which was further purified by recrystallization from n-pentane: m.p. 54–55°C, $[\alpha]_D^{23}$ +35.68° (*c* 10, benzene) (Lit. [13] $[\alpha]_D^{23}$ −35.7° (*c* 10, benzene)), > 99% ee by capillary GC of its *N*-trifluoroacetyl-*S*-(−)prolyl [17] derivative.

Upgrading the optical purity of ethyl exo-norbornylisopinocampheylborinate via l-proline. Norbornene (25 mmol) was hydroborated with Ipc_2BH (25 mmol, derived from (−)-α-pinene) at −25°C according to the literature procedure [7]. The trialkylborane obtained was treated with 5 ml of water, followed by 2.8 ml (50 mmol) of chilled acetaldehyde added via a syringe. The reaction mixture was stirred overnight and excess acetaldehyde pumped off under reduced pressure. The borinate (^{11}B NMR δ +52 ppm) thus obtained was dried over anhydrous Na_2SO_4 and filtered. From the borinate (5.8 g, 20 mmol), the *l*-proline adduct was prepared as reported previously. The adduct was recrystallized from methanol/THF to give the crystalline derivative: 3.6 g, 50% yield. The chelate (3.6 g, 10 mmol) was treated with 8 ml of 3 *M* hydrochloric acid to remove proline. The THF layer was separated and dried over Na_2SO_4. To it was added 1.3 ml (20 mmol) of acetaldehyde and the reaction mixture was stirred overnight. Excess acetaldehyde was removed and the borinic acid re-esterified with methanol according to the standard procedure to give the methyl boronate: b.p. 45–47°C/1.0 mmHg $[\alpha]_D^{23}$ −26.5° (*c* 7, methanol) (Lit. [7] $[\alpha]_D^{23}$ −26.47° (*c* 7, MeOH)). Oxidation of the boronate by alkaline hydrogen peroxide gave *exo*-norborneol, which was then further purified by preparative GC to give GC pure material: m.p. 125–126°C, $[\alpha]_D^{23}$ +5.2 (*c* 7.5, EtOH) in 100% ee (Lit. [7] $[\alpha]_D^{23}$ +5.17° (*c* 7.5, EtOH)).

Upgrading the optical purity of ethyl 3-tetrahydropyranylboronate. 3,4-Dihydro-2*H*-pyran (25 mmol) was hydroborated with diisopinocampheylborane (25 mmol,

derived from (+)-α-pinene), as described in the literature [7]. The trialkylborane (^{11}B NMR δ +86 ppm) thus obtained was treated with 5.6 ml (100 mmol) of chilled acetaldehyde (added with the aid of a syringe) and the reaction mixture was stirred at 25°C for 6 h. Excess acetaldehyde and liberated α-pinene were removed under reduced pressure. Iminodiacetic acid (2.7 g, 20 mmol) was taken in 30 ml of DMSO. To it diethyl 3-tetrahydropyranylboronate of 83% ee (3.72 g, 20 mmol) in 5 ml of THF was added and the reaction mixture stirred at 100–120°C for 2–3 h. Following completion of the reaction, the solvents were evaporated under vacuum and the residue was treated with methanol to give a white crystalline solid. This was recrystallized with DMSO at 0°C to give 2.2 g, 48% yield, m.p. 220–223°C (d). The solid was suspended in 25 ml of THF and treated with 2.5 ml of 6 *M* hydrochloric acid. The organic layer was separated, and reesterified with methanol to give dimethyl 3-tetrahydropyranylboronate, $[\alpha]_D^{23}$ −20.42° (*c* 5.9, MeOH). The boronate thus obtained was oxidized with 3 *N* sodium hydroxide and 30% hydrogen peroxide in the usual manner. The alcohol was distilled: b.p. 90–91°C/20 mmHg. It was further purified by preparative GC to obtain GC pure material: $[\alpha]_D^{23}$ +11.86° (neat) (Lit. [7] $[\alpha]_D^{23}$ +11.9° (neat)), > 99% ee.

Data for the yields, ^{11}B NMR spectra and the m.p's are summarized in Tables 1 and 2.

Acknowledgement

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References

1 R.L. Letsinger, I.K. Skoog and N. Remes, J. Am. Chem. Soc., 76 (1954) 4047.
2 R.L. Letsinger and N. Remes, J. Am. Chem. Soc., 77 (1955) 2489.
3 J.A. Sinclair, G.A. Molander and H.C. Brown, J. Am. Chem. Soc., 99 (1977) 954.
4 G.H.L. Nefkens and B. Zwanenburg, Tetrahedron, 39 (1983) 2995.
5 P.M. Gallop, M.A. Paz and E. Henson, Science, 217 (1982) 166.
6 C.J. Strang, E. Henson, Y. Okamoto, M.A. Paz and P.M. Gallop, (manuscript communicated 1986).
7 H.C. Brown and J.V.N. Vara Prasad, J. Org. Chem., 51 (1986) 4526.
8 T. Mancilla, R. Contreras and B. Wrackmeyer, J. Organomet. Chem., 307 (1986) 1.
9 T. Mancilla and R. Contreras, J. Organomet. Chem., 321 (1987) 191.
10 S. Masamune, B.M. Kim, J.S. Peterson, T. Sato, S.J. Veenstra and T. Imai, J. Am. Chem. Soc., 107 (1985) 4549.
11 H.C. Brown, N.G. Bhat and V. Somayaji, Organometallics, 2 (1983) 1311.
12 H.C. Brown, J.V.N. Vara Prasad, A.K. Gupta and R.K. Bakshi, J. Org. Chem., 52 (1987) 310.
13 H.C. Brown and N.M. Yoon, Israel J. Chem., 15 (1976/77) 12.
14 H.C. Brown, G.W. Kramer, A.B. Levy and M.M. Midland, Organic Syntheses via Boranes, Wiley-Interscience; New York, 1975.
15 H.C. Brown, A.K. Mandal and S.U. Kulkarni, J. Org. Chem., 42 (1977) 1392.
16 H.C. Brown and B. Singaram, J. Org. Chem., 49 (1984) 945
17 W.A. Bonner, J. Chromatogr. Sci., 10 (1972) 159.