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Formal and improved synthesis of enantiopure chiral methanol

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ABSTRACT

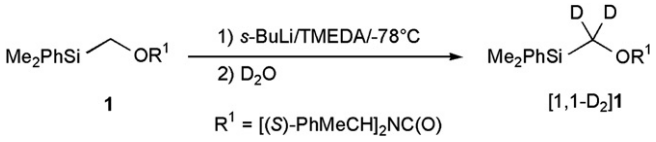
[D_2]Methanol was converted to the carbamate derived from 2,2,6,6-tetramethylpiperidine. It was metalated with *s*-BuLi/TMEDA at −78 °C with a high primary kinetic isotope effect to give an α-oxymethyllithium, which was silylated with chlorodimethylphenylsilane. The silylmethyl carbamate formed was lithiated and borylated with the borate derived from *tert*-butanol and (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol to give diastereomeric boronates, which were separated by preparative HPLC and can in principle be converted to enantiopure chiral methanols. Thus, both enantiomers are easily accessible in nine linear steps.

1. Introduction

The synthesis of chiral acetic acid by two independent groups led by Cornforth[1] and Arigoni[2,3] marked the beginning of the use of the chiral methyl group for the elucidation[4] of chemical and enzymatic reaction mechanisms. We have recently reported the synthesis of the tosylates of enantiopure chiral methanols (CHDTOH) in a total of 12 steps for both enantiomers, starting from commercially available starting materials.[5] These tosylates are a much more convenient source for chiral methyl groups than the *N*,*N*-ditosylmethylamines derived from the respective chiral acetic acids. We have already used these tosylates of chiral methanol for the alkylation of homocysteine to prepare methionines with chiral CHDT groups at sulfur.

2. Results and discussion

For the sake of clarity and in order to pinpoint the steps in the synthesis of the chiral methanols amenable to improvement, their synthesis is given here.[5] Carbamate **1** prepared from (dimethylphenylsilyl)methanol and homochiral (*S*,*S*)-bis(1-phenylethyl)amine had to be deuterated by four cycles of metalation with *s*-BuLi/TMEDA and quenching with D_2O, with purification of product after every two cycles (Scheme 1). Lithiation of [1,1-D_2]**1** and borylation with the mixed boric acid ester **2** derived from (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol and *tert*-butanol gave a mixture of deuterated diastereomeric boronates **3** and **4** in a ratio of 1.2:1 (Scheme 2). They were separated and stereospecifically reduced with $LiBEt_3T$ with inversion of configuration to give boronates **5**, which were oxidized to the D- and T-labeled (dimethylphenylsilyl)methanols **6**. Base-induced Brook rearrangement, the key step of the synthesis, furnished chiral methanols **7**, which were isolated in high yield as their respective tosylates. Their enantiomeric excesses of 98% were determined by ^{3}H NMR spectroscopy after transfer of the methyl groups to the nitrogen of (*S*)-2-methylpiperidine.



Scheme 1. Synthesis of dideuterated carbamate **1**.

To shorten and improve the synthesis, we wanted to replace the laborious deuteration of **1** by the use of methanol CD_3OD, necessitating a change of strategy at the beginning. Furthermore, we were looking for a deuterated substrate derived from an achiral precursor to additionally save (*S*,*S*)-bis(1-phenylethyl)amine as a chiral auxiliary. As the experiments with chiral methyl groups are performed with both enantiomers routinely for complementarity, the diastereoselectivity of the borylation is not critical. Preferably, it should be close to 1. Naturally, the boronates should be stable for storage.

We envisaged three achiral substrates for borylation, triphenylacetate [1,1-D_2]**9**, and carbamates [1,1-D_2]**10** as well as [1,1-D_2]**11** prepared from the corresponding methyl esters by metalation and silylation (Fig. 1). Methyl carbamate [1,1,1-D_3]**8** was not considered a suitable precursor for [1,1-D_2]**1**, as metalation would very likely occur at the benzylic position preferably.

It was found by Beak et al.[6] and Seebach et al.[7] that the methyl esters and secondary amides derived from substituted benzoic acids and triphenylacetic acid, having shielded carbonyl groups, could be metalated using *s*-BuLi/TMEDA and that the intermediate

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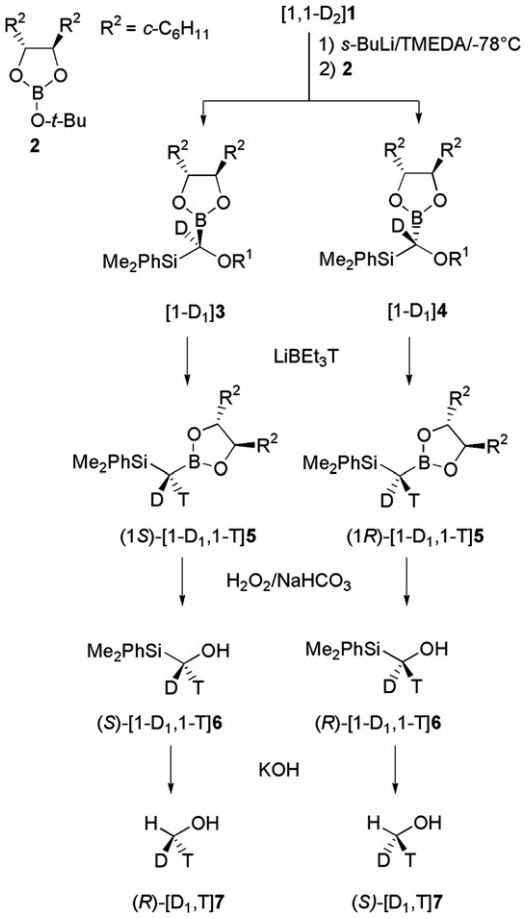


Scheme 2. Synthesis of chiral methanols from dideuterated carbamate **1**.

α-heteroatom-substituted alkyllithiums reacted with electrophiles. With this information in mind, we performed experiments in the unlabeled series first. (Dimethylphenylsilyl)methanol and triphenylacetic acid were converted to the silylmethyl ester **9** in 91% yield by the Mitsunobu reaction using triphenylphosphine/diisopropyl azodicarboxylate (DIAD) in toluene (Scheme 3).[8] The lithiation of ester **9** proceeded more slowly (90 min) than that of carbamate [1-D]**1** (15 min). Borylation of the intermediate oxymethyllithium (±)-**14** was borylated with mixed borate **2**.[5] As the oxymethyllithium was configurationally labile, even at −95 °C, and enantiomerization was faster than borylation, one of the diastereomeric boronates was formed selectively (combined yield: 52%, **15**/**16** 3.3:1). Two flash chromatographies were necessary to get homogenous diastereomers, as starting ester and minor diastereomer **16** were of similar polarity. The (*R*) configuration at the newly formed stereogenic center of the major diastereomer **15** was determined by chemical correlation. It was reduced with $LiAlD_4$ to boronate (1*R*)-[1-D_1]**5**, followed by oxidative cleavage of the C–B bond to give

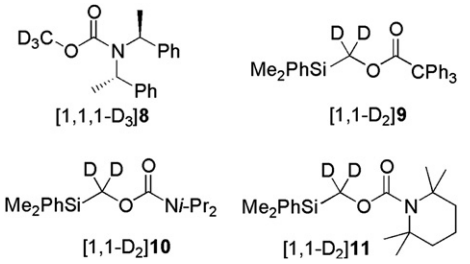
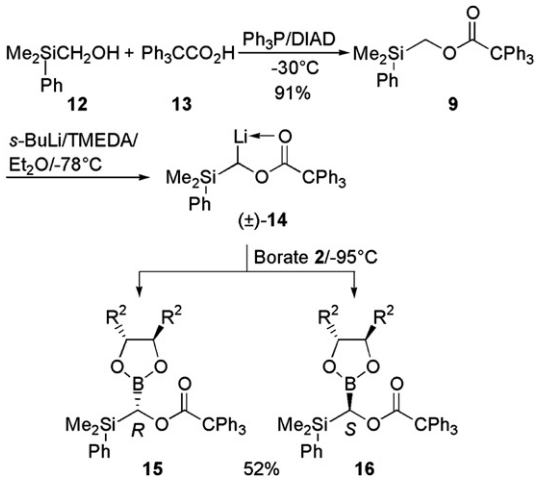


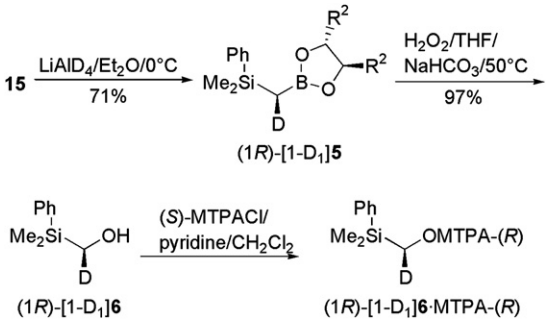
Figure 1. Envisaged precursors for the synthesis of chiral methanols.



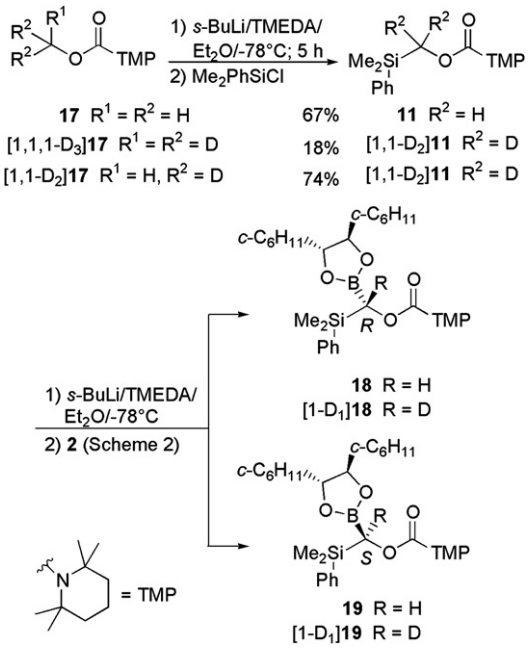
Scheme 3. Preparation of boronates **15** and **16** from silylmethyl ester **9**.

deuterated silylmethanol (1*R*)-[1-D_1]**6** (Scheme 4).[5] Its (*R*) configuration was secured by recording the ^1H NMR spectrum of the corresponding (*R*)-Mosher ester[5] and comparing it with the spectra of authentic samples of (1*R*)- and (1*S*)-[1-D_1]**6**. The enantiopurity (99% ee) proved that reduction of **15** with $LiAlD_4$ and oxidative cleavage of the B–C bond followed stereospecifically an invertive and retentive course, respectively.[5] Unfortunately, the triphenylacetic acid derivatives were chemically somewhat labile, especially toward *s*-BuLi, so that their use had to be abandoned. Therefore, we returned to the two left precursors [1,1-D_2]**10** and [1,1-D_2]**11** in Figure 1. A literature search revealed that Boche et al. had metalated methyl *N*,*N*-diisopropylcarbamate with *s*-BuLi/TMEDA for 5 h at −78 °C and quenched the intermediate oxymethyllithium with tributylchlorostannane to give the corresponding tributylstannylmethyl carbamate in 43% yield.[9] We were anticipating a similar low yield for the silylation with chlorodimethylphenylsilane. Furthermore, we feared that the diastereomeric boronates obtained from the lithiated silylmethyl carbamate could not be separated, as the *N*,*N*-diisopropylcarbamoyl group seemed to be too small to allow that, based on previous experience. Carbamate [1,1-D_2]**11** derived from 2,2,6,6-tetramethylpiperidine (TMPH) and reminiscent of the carbamates[10] used by Hoppe et al. to protect primary alcohols for metalation seemed to be a feasible alternative to [1,1-D_2]**10**. Unlabeled carbamate **11** has recently been metalated and stannylated to access (*R*)- and (*S*)-(tributylstannyl)-[D_1]methanol.[11]

As before, the transformations were performed first in the unlabeled series to optimize the reaction conditions, starting from methyl carbamate[12] **17** a known compound easily accessible from methyl chloroformate and TMPH. Thus, **17** was metalated[11] with *s*-BuLi/TMEDA in dry Et_2O at −78 °C for 4 h and the intermediate oxymethyllithium was reacted with chlorodimethylphenylsilane to



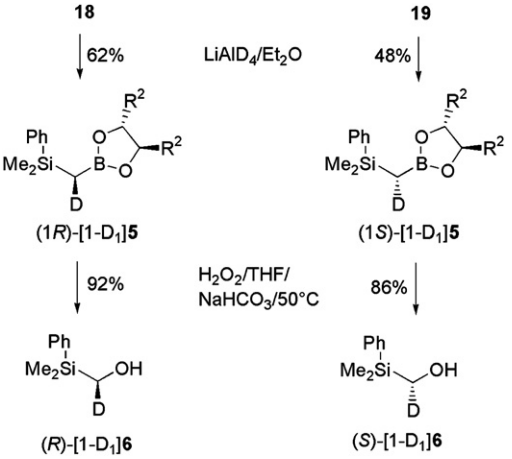
Scheme 4. Determination of configuration at C-1 (boron bearing carbon atom) of major diastereomer **15**.



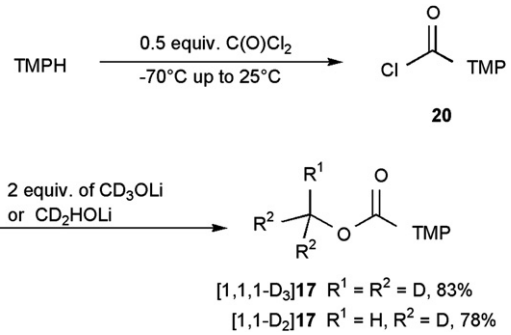
Scheme 5. Metalation of carbamates **17** and borylation with borate **2**.

give silylmethyl carbamate **11** in 67% yield (Scheme 5). It was metalated again with *s*-BuLi/TMEDA in dry Et_2O at −78 °C for 45 min and the α-oxy-α-silylmethyllithium was borylated with borate **2**. The mixture of boronates was separated easily by preparative HPLC to give diastereomers **18** (t_R 8.8 min), the major and more polar one, and **19** (t_R 5.4 min), in yields of 57% and 31% (corresponding to a ratio of 1.8:1), respectively. When the α-oxy-α-silylmethyllithium was borylated at −40 °C, the ratio decreased to 1.5:1 suffient for the labeled series. To determine the configuration at the new stereogenic center, both boronates were reduced with $LiAlD_4$ in an S_N2 type reaction to deuterated boronates (1*R*)- and (1*S*)-[1-D_1]**5** in yields of 62% and 48%, respectively (Scheme 6).[5] Oxidation with $H_2O_2/NaHCO_3$ at 50 °C furnished the respective (dimethylphenylsilyl)methanols (*S*)- and (*R*)-[1-D_1]**6** in high yields with enantiomeric excesses of 99% as proven by ^{1}H NMR spectroscopy of their (*R*)-Mosher esters.[5]

Now we wanted to repeat the sequence with the triply deuterated methyl carbamate [1,1,1-D_3]**17**, derived from CD_3OD. Its synthesis was performed as given in Scheme 7. The reaction



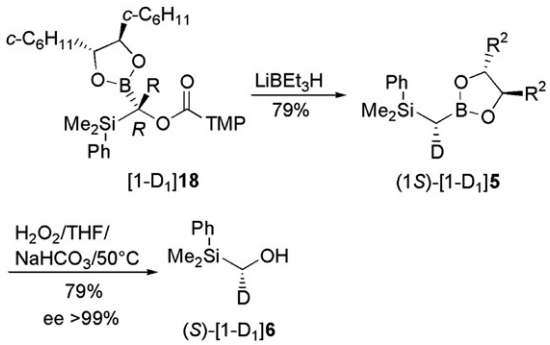
Scheme 6. Determination of configuration of boronates **18** and **19** and of ee of silylmethanols **6**.



Scheme 7. Preparation of methyl carbamates [1,1,1-D_3]**17** and [1,1-D_2]**17**.

mixture containing carbamoyl chloride[13] **20** was treated with 2 equiv of CD_3OLi prepared from CD_3OD and *n*-BuLi in dry THF. Work up furnished the desired carbamate [1,1,1-D_3]**17** purified by bulb-to-bulb distillation. The next step on the way to chiral silylmethanol was the silylation of the carbamate, which did not give the required [1,1-D_2]**13** in satisfactory yield, unfortunately (see Scheme 5). The primary kinetic isotope effect, known to be very high in such a case, was detrimental for the yield.[14] It was at best 18% after metalation for 72 h at −78 °C using the conditions as used for the preparation of the unlabeled species.

Therefore, we prepared the doubly deuterated methyl carbamate [1,1-D_2]**17** from commercially available CHD_2OH similarly. Metalation of [1,1-D_2]**17** with 1.3 equiv of *s*-BuLi/TMEDA at −78 °C for 18 h, followed by silylation, furnished carbamate [1,1-D_2]**11** in 74% yield (Scheme 5), containing monodeuterated species (3.3%, corresponding to a $k_H/k_D>30$ assuming a CD_2HOH with D_2 of 100%, it was however only 98%) as determined by ^{1}H NMR spectroscopy (400 MHz). Metalation and borylation as in the unlabeled series, afforded a mixture of [1-D_1]**18** and [1-D_1]**19** (ratio in crude product by ^{1}H NMR spectroscopy: 1.7:1), which were separated by HPLC (yield of [1-D_1]**18**: 44%; yield of [1-D_1]**19**: 26%). Each of the two diastereomers contained less than 0.2% of the unlabeled species, demonstrating that the deprotonation of the silylmethyl carbamate showed an estimated primary kinetic isotope effect of 20–30. Finally, major boronate [1-D_1]**18** was exemplarily reduced with $LiBEt_3H$ to (1*S*)-[1-D_1]**5** in 79% yield, compared to 62% when using $LiAlD_4$ (Scheme 8). Oxidative cleavage of the the B–C bond furnished silylmethanol (*S*)-[1-D_1]**6** in again 79% yield with an ee>99% as determined by ^{1}H NMR spectroscopy of the (*R*)-Mosher ester. Similarly, boronate [1-D_1]**19** will yield the (*S*)-silyl-[D_1]methanol. To obtain the enantiopure chiral methanols, the diastereomeric boronates [1-D_1]**18** and [1-D_1]**19** will have to be reduced with $LiBEt_3T$ and oxidized to deuterated and tritiated silylmethanols undergoing Brook rearrangement to chiral methanols as described recently.[5]



Scheme 8. Conversion of boronate [1-D_1]**18** to silylmethanol (*S*)-[1-D_1]**6**.

3. Conclusions

In summary, we have shown that CD_2HOH can be used efficiently to prepare the carbamate derived from TMPH, amenable to lithiation and silylation. The resulting dideuterated silylmethyl carbamate was converted to diastereomeric boronates, which can be easily converted to chirally deuterated silylmethanols. Two high primary kinetic isotope effects ensure complete removal of protium from the boron bearing carbon atom. This approach represents a formal synthesis of enantiopure chiral methanols in a total of nine linear steps, starting from CD_2HOH.

4. Experimental

4.1. General information

^1H and ^{13}C NMR (*J* modulated) spectra were measured in $CDCl_3$ at 300 K on a Bruker Avance DRX 400 at 400.13 MHz and 100.61 MHz, respectively. Chemical shifts, given in parts per million, were referenced to residual $CHCl_3$ (δ_H=7.24) and $CDCl_3$ (δ_C=77.00). The signal of the boron bearing carbon atom in boronates was normally not detected in the ^{13}C NMR spectra.[15] IR spectra were run on a Perkin–Elmer 1600 FT-IR spectrometer; liquid samples were measured as films on a silicon disc.[16] Analytical HPLC was performed on a Jasco System (PU-980 pump, UV 975 and RI 930) using a Superspher Si 60 (4 μm) column (∅ 0.4×25 cm), 5% EtOAc/hexanes, 2 mL/min, 20 °C, UV 254 nm; t_R=5.4 min (**18**) and 8.8 min (**19**). Preparative HPLC was performed on a Dynamax Model SD-1 equipped with a Model UV-1 absorbance detector using a Superspher Si 60 (4 μm) column (∅ 3.2×23.7 cm), 5% EtOAc/hexanes, 80 mL/min, 20 °C; t_R=9.0 and 12.0 min. Optical rotations were measured at 20 °C on a Perkin–Elmer 351 polarimeter in a 1 dm cell. TLC was carried on 0.25 mm thick Merck plates, silica gel 60 F_{254}. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualized by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (23.0 g) and of $Ce(SO_4)_2\cdot 4H_2O$ (1.0 g) in 10% aqueous H_2SO_4 (500 mL), followed by heating with a heat gun. Melting points were determined on a Reichert Thermovar instrument and were uncorrected.

As the nomenclature of boronates is complex, the practical system of Matteson et al. was adopted.[17]

4.2. (Dimethylphenylsilyl)methyl triphenylacetate (9)

Diisopropyl azodicarboxylate (1.18 mL, 1.212 g, 6 mmol) was added dropwise to a stirred mixture of triphenylphosphine (1.574 g, 6 mmol), triphenylacetic acid (**13**) (1.586 g, 5.5 mmol), and (dimethylphenylsilyl)methanol (**12**) (0.831 g, 5 mmol) in dry toluene (12.5 mL) under argon at −30 °C. The cooling bath was removed and the mixture was stirred at ambient temperature until completion of the reaction (2 h). The reaction mixture was concentrated. The residue was purified by flash chromatography (hexanes/CH_2Cl_2 1:1; R_f 0.24 for hexanes/CH_2Cl_2 2:1) to afford ester **9** (1.98 g, 91%), which was crystallized from hexanes; mp 61–62 °C. IR (Si): 3058, 2958, 1731, 1494, 1446, 1282, 1251, 1182, 1116 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 7.40–7.12 (m, 20H), 4.07 (s, 2H), 0.19 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.5, 143.0, 136.0, 133.8, 130.3, 129.4, 127.8, 127.6, 126.7, 67.6, 58.0, −4.7. Anal. Calcd for $C_{29}H_{28}O_2Si$: C, 79.77; H, 6.46. Found: C, 79.72; H, 6.63.

4.3. (*R*,*R*)-1,2-Dicyclohexylethane-1,2-diol (1*R*)- and (1*S*)-[triphenylacetoxy-(dimethylphenylsilyl)methyl]-boronate (15 and 16)

s-BuLi (2.31 mL, 3 mmol, 1.3 M in cyclohexane) was added dropwise to a stirred solution of triphenylacetate **9** (0.873 g, 2 mmol) and TMEDA (0.349 g, 0.45 mL, 3 mmol) in dry Et_2O (10 mL) at −78 °C under argon. After stirring for 90 min at −78 °C, the reaction mixture was cooled to −95 °C and a solution of the mixed borate[5] **2** [prepared from 0.747 g (3.3 mmol, crystallized from 1,2-dichloroethane, ee 99%) of (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol and (*t*-BuO)$_3$B (0.868 g, 1.07 mL, 3.77 mmol)] dissolved in dry Et_2O (5 mL). After stirring for 2 h at −95 °C, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and Et_2O (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product [**15**/**16**/**9** 3.3:1:0.5 by ^1H NMR; CHSi: 4.25 (**15**), 4.19 (**16**), and 4.05 (**9**)] was flash chromatographed [hexanes/CH_2Cl_2 2:1; for TLC 2:1: R_f 0.53 for **16**, 0.49 for **9**, and 0.42 for **15**] to give a mixture of boronate **16** and ester **9** (0.12 g) and boronate **15** (0.62 g, 46%), which was crystallized from hexanes; mp 140–142 °C; $[\alpha]_D^{20}$ +13.1 (*c* 1.01, acetone). The mixture of **16** and **9** was separated by flash chromatography (hexanes/CH_2Cl_2 3:1) to give **16** as a colorless gum; $[\alpha]_D^{20}$ +32.1 (*c* 2.0, acetone).

4.3.1. Compound *15*

IR (Si): ν_{max} 2925, 2852, 1726, 1448, 1352, 1262, 1185 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 7.35–7.16 (m, 20H), 4.19 (s, H), 3.80 (m, 2H), 1.74–1.49 (m, 10H), 1.24–1.02 (m, 8H), 1.02–0.78 (m, 4H), 0.18 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.6, 143.2, 136.3, 134.0, 130.4, 129.1, 127.6, 127.5, 126.5, 84.3, 67.3, 42.9, 28.7, 27.6, 26.4, 26.0, 25.8, −4.3, −4.5. Anal. Calcd for $C_{43}H_{51}BO_4Si$: C, 77.00; H, 7.66. Found: 76.78; H, 7.63.

4.3.2. Compound *16*

IR (Si): ν_{max} 2925, 2853, 1728, 1448, 1354, 1259, 1182 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 7.34–7.16 (m, 20H), 4.26 (s, H), 3.78 (m, 2H), 1.70 (m, 8H), 1.56 (m, 2H), 1.17 (m, 8H), 1.00 (m, 2H), 0.88 (m, 2H), 0.24 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.5, 143.4, 136.4, 134.0, 130.5, 129.1, 127.5, 126.4, 84.1, 67.5, ∼60 (very broad, BCH?), 42.8, 28.7, 27.5, 26.4, 26.0, 25.8, −3.8, −5.0. Anal. Calcd for $C_{43}H_{51}BO_4Si$: C, 77.00; H, 7.66. Found: 77.02; H, 7.78.

4.4. (*R*,*R*)-1,2-Dicyclohexylethane-1,2-diol (1*R*)-(dimethylphenylsilyl)-[1-D_1]methylboronate {(1*R*)-[1-D_1]5} from 15

Boronate **15** (0.671 g, 1 mmol) was reduced with $LiAlD_4$ according to General Procedure A given in Ref. 5 to give (1*R*)-[1-D_1]**5** (0.275 g, 71%). The ^1H NMR spectrum was identical with that of an authentic sample.

4.5. (*R*)-(Dimethylphenylsilyl)-[1-D_1]methanol {(*R*)-[1-D_1]6}

Boronate (1*R*)-[1-D_1]**5** (0.190 g, 0.493 mmol) was oxidized by General Procedure B given in Ref. 5 to yield silylmethanol (*R*)-[1-D_1]**6** (80 mg, 97%) as a colorless liquid.

4.6. Preparation of methyl 2,2,6,6-tetramethylpiperidine-1-carboxylates {17, [1,1,1-D_3]17 and [1,1-D_2]17}

4.6.1. Improved preparation of *17*

A mixture of TMPH (7.4 mL, 43.86 mmol) and methyl chloroformate (3.7 mL, 43.86 mmol) in dry THF (20 mL) was heated at 40 °C (48 h). Water (40 mL) was added and the mixture was stirred for 5 min. The organic phase was separated and the aqueous one extracted with EtOAc (3×15 mL). The combined organic layers were washed with HCl (40 mL, 2 M), a saturated aqueous solution of $NaHCO_3$ (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (110–120 °C/13 mbar) to yield carbamate (3.00 g, 73% compared to

30–40% in Et_2O according to the literature procedure[12]) as a colorless liquid.

^1H NMR (400.1 MHz, $CDCl_3$): δ 3.61 (s, 3H), 1.67–1.56 (m, 6H), 1.37 (s, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): 157.9, 56.0 (2C), 50.9, 39.4 (2C), 29.8 (4C), 15.5.

4.6.2. [D_3]Methyl 2,2,6,6-tetramethylpiperidine-1-carboxylate {[1,1,1-D_3]**17**}

A solution of 2,2,6,6-tetramethylpiperide-1-carbonyl chloride was prepared from phosgene (4.85 mL, 9.37 mmol, approx. 20% solution in toluene) according to General Procedure given in Ref. 13 for the "Synthesis of 2,2,6,6-Tetramethylpiperidine Urethanes" in the literature, except that a two-necked round-bottomed flask fitted with an argon balloon was used. Instead of filtering the mixture it was cooled to −50 °C and a solution of CD_3OLi in THF was added. It had been prepared by addition of *n*-BuLi (11.7 mL, 18.72 mmol, 1.6 M in hexanes) to a stirred solution of CD_3OD (0.675 g, 18.72 mmol, 0.68 mL) in dry THF (20 mL) under argon at ambient temperature. Stirring was continued for 30 min at −50 °C and 1 h at ambient temperature. Water (25 mL) and HCl (5 mL, 2 M) were added. The organic phase was separated and the aqueous one extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were washed with water (3×20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was bulb-to-bulb distilled (100–105 °C/9 mbar) to give methyl carbamate [1,1,1-D_3]**17** (1.547 g, 82%).

The ^1H and ^{13}C NMR spectra were identical with that of the unlabeled species, except for the missing signals for OCH_3.

4.6.3. [D_2]Methyl 2,2,6,6-tetramethylpiperidine-1-carboxylate {[1,1-D_2]**17**}

It was prepared similarly to the trideuterated species, starting from the same amount of phosgene in toluene, but using CD_2HOH (0.638 g, 18.72 mmol, 0.76 mL; 98% D_2) instead of CD_3OD, to yield dideuterated carbamate [1,1-D_2]**17** (1.46 g, 78%).

^1H NMR (400.1 MHz, $CDCl_3$): δ 3.73 (t, J=1.5 Hz, $OCDH_2$, 1%), 3.58 (quint, J=1.5 Hz, 1H, OCD_2H, 99%), 1.68–1.55 (m, 6H), 1.37 (s, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 157.9, 56.0 (2C), 50.4 (quint, J=22.2 Hz, OCD_2H), 39.4 (2C), 29.8 (4C), 15.5.

4.7. Preparation of (dimethylphenylsilyl)methyl 2,2,6,6-tetramethylpiperidine-1-carboxylates {11 and [1,1-D_2]11}

4.7.1. (Dimethylphenylsilyl)methyl 2,2,6,6-tetramethylpiperidine-1-carboxylate (**11**)

s-BuLi (4.28 mL, 6 mmol, 1.4 M solution in cyclohexane) was added dropwise to a stirred solution of methyl carbamate **17** (0.996 g, 5 mmol) and dry TMEDA (0.697 g, 0.91 mL, 6 mmol) in dry Et_2O (10 mL) at −78 °C under argon. After stirring for 4 h at −78 °C, chlorodimethylphenylsilane (1.024 g, 1.0 mL, 6 mmol) was added, and the reaction mixture was stirred and allowed to warm to room temperature in the cooling bath. After addition of a saturated aqueous solution of sodium bicarbonate (20 mL), the organic phase was separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was first purified by flash chromatography (CH_2Cl_2/hexanes 15:1, R_f 0.35) and finally bulb-to-bulb distilled (110–112 °C/0.3 mbar) to give silylmethyl carbamate **11** (1.118 g, 67%) as a colorless oil.

IR (Si): ν_{max} 2963, 2942, 1690, 1365, 1333, 1323, 1302, 1076 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 7.53 (m, 2H), 7.32 (m, 3H), 3.92 (s, 2H), 1.59 (m, 6H), 1.32 (s, 12H), 0.36 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.4, 136.8, 133.8 (2C), 129.3, 127.8 (2C), 56.1, 56.0 (2C), 39.6 (2C), 29.7 (4C), 15.5, −4.0 (2C). Anal. Calcd for $C_{19}H_{31}NO_2Si$ (333.55): C, 68.42; H, 9.37; N, 4.20. Found: C, 68.13; H, 9.21; N, 4.09.

4.7.2. (Dimethylphenylsilyl)-[D_2]methyl 2,2,6,6-tetramethylpiperidine-1-carboxylate {[1,1-D_2]**11**} from [1,1,1-D_3]**17**

s-BuLi (4.24 mL, 5.93 mmol, 1.5 equiv, 1.4 M solution in cyclohexane) was added dropwise to a stirred solution of methyl carbamate [1,1,1-D_3]**17** (0.787 g, 3.95 mmol) and TMEDA (0.689 g, 0.89 mL, 5.93 mmol, 1.5 equiv) in dry Et_2O (3.1 mL) at −78 °C under argon. After stirring for 72 h at −78 °C, chlorodimethylphenylsilane (1.012 g, 1.0 mL, 5.93 mmol, 1.5 equiv) was added, and the reaction mixture was allowed to warm to room temperature for 18 h. Work up and purification as for the unlabeled compound gave deuterated silylmethyl carbamate [1,1-D_2]**11** (0.237 g, 18%).

^1H and ^{13}C NMR spectra were identical with that of the unlabeled species, except for the missing signals for OCH_2Si.

4.7.3. (Dimethylphenylsilyl)-[D_2]methyl 2,2,6,6-tetramethylpiperidine-1-carboxylate {[1,1-D_2]**11**} from [1,1-D_2]**17**

s-BuLi (2.01 mL, 2.82 mmol, 1.3 equiv, 1.4 M solution in cyclohexane) was added dropwise to a stirred solution of dideuterated methyl carbamate [1,1-D_2]**17** (0.437 g, 2.17 mmol) and TMEDA (0.328 g, 0.43 mL, 2.82 mmol, 1.3 equiv) in dry Et_2O (2.17 mL) at −78 °C under argon. After stirring for 18 h at −78 °C, chlorodimethylphenylsilane (0.47 mL, 2.82 mmol, 1.3 equiv) was added and the reaction mixture was stirred while warming up to room temperature within 3 h. Work up and purification as for the unlabeled compound gave deuterated silylmethyl carbamate [1,1-D_2]**11** (0.540 g, 74%).

IR (Si): ν_{max} 2964, 1689, 1366, 1331, 1298, 1250, 1116, 1082 cm^{-1}. The ^1H NMR spectrum was identical with that of the unlabeled species, except for the missing signal for OCH_2Si. It contained 3.3% of mondeuterated species: 3.90 (t, J=1.5 Hz, OCDHSi); ^{13}C NMR spectrum was identical with that of unlabeled species, except for the signal for OCH_2Si, which was replaced by the resonance for OCDHSi: 55.5 (quint, J=20.6 Hz).

4.8. (*R*,*R*)-1,2-Dicyclohexylethane-1,2-diol [(1*S*)- and (1*R*)-(2,2,6,6-tetramethylpiperidine-1-carbonyloxy)-(dimethylphenylsilyl)methyl]boronates {18 and 19, [1-D_1]18 and [1-D_1]19}

4.8.1. Preparation of **18** and **19**

A solution of silylmethyl carbamate **11** (1.004 g, 3.01 mmol) and dry TMEDA (0.419 g, 0.54 mL, 3.61 mmol) in dry Et_2O (9 mL) was cooled to −78 °C under argon. *s*-BuLi (2.58 mL, 3.61 mmol, 1.4 M solution in cyclohexane) was added and after stirring for 1 h, the freshly prepared[5] boric acid ester **2** (3.61 mmol) dissolved in dry Et_2O (4.5 mL) was added. Stirring was continued for 1 h at −78 °C. The reaction was quenched with a mixture of saturated aqueous solutions of NH_4Cl and $NaHCO_3$ (1:1, 40 mL). The organic phase was separated and the aqueous layers were extracted with Et_2O (3×40 mL). The combined organic phase were dried ($MgSO_4$), concentrated, and purified by flash chromatography (hexanes/EtOAc 10:1, R_f 0.45/0.33) to give a mixture of diastereomers **18** and **19** in a ratio of 1.8:1 (^1H NMR), which were separated by preparative HPLC (EtOAc/hexanes 1:19; **19**: t_R 5.5 min; **18**: t_R 8.8 min) to give boronate **18** (0.527 g, 31%) and **19** (0.973 g, 57%) as colorless oils.

*4.8.1.1. Compound **18**.* $[\alpha]_D^{20}$ +27.8 (*c* 1.3, acetone); IR (Si): ν_{max} 2924, 2878, 1680, 1590, 1428, 1164 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 7.63 (m, 2H), 7.29 (m, 3H), 3.80 (s, 1H), 3.50 (m, 2H), 1.86–1.78 (m, 2H), 1.72–1.49 (m, 14H), 1.35 (s, 6H), 1.31 (s, 6H), 2.03–1.03 (m, 8H), 0.97–0.83 (m, 4H), 0.36 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.8, 138.2, 134.4 (2C), 128.8, 127.4 (2C), 82.7 (2C), 58.2 (2C), 43.1 (2C), 40.7 (2C), 29.6 (2C), 29.5 (2C), 29.2 (2C), 28.6 (2C), 26.8 (2C), 26.3 (2C), 26.2 (2C), 15.6, −3.7, −3.9. Anal. Calcd

for $C_{33}H_{54}BNO_4Si$ (567.68): C, 69.82; H, 9.59; N, 2.47. Found: C, 69.60; H, 9.39; N, 2.33.

*4.8.1.2. Compound **19**.* $[\alpha]_D^{20}$ +14.7 (*c* 1.1, acetone); IR (Si): ν_{max} 2924, 2852, 1679, 1590, 1428, 1165 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.29 (m, 3H), 3.88 (s, 1H), 3.52 (m, 2H), 1.98–1.90 (m, 2H), 1.74–1.50 (m, 14H), 1.35–1.22 (m, 2H), 1.33 (s, 6H), 1.30 (s, 6H), 1.29–1.03 (m, 6H), 1.02–0.85 (m, 4H), 0.39 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.3, 138.8, 134.0 (2C), 128.7, 127.5 (2C), 82.7 (2C), 58.5 (2C), 43.1 (2C), 40.8 (2C), 29.7 (2C), 29.5 (2C), 29.3 (2C), 29.1 (2C), 26.7 (2C), 26.3 (2C), 26.1 (2C), 15.6, −3.8, −4.1, BCHSi not detected. Anal. Calcd for $C_{33}H_{54}BNO_4Si$ (567.68): C, 69.82; H, 9.59; N, 2.47. Found: C, 69.70; H, 9.45; N, 2.32.

*4.8.2. Preparation of [1-D_1]**18** and [1-D_1]**19***

Dideuterated silylmethyl carbamate [1,1-D_2]**11** (1.117 g, 3.33 mmol) was converted to a mixture of deuterated diastereomers by the procedure used for the nondeuterated species. The crude product was purified with flash chromatography to give a mixture of the diastereomers [1.466 g, ratio 1.8:1 (by ^1H NMR)] as a colorless oil. The mixture was separated by HPLC to give the individual diastereomers {[1-D_1]**18**: 0.899 g, 47%; [1-D_1]**19**: 0.490 g, 26%}.

*4.8.2.1. Compound [1-D_1]**18**.* $[\alpha]_D^{20}$ +27.8 (*c* 1.3, acetone); H at boron bearing carbon atom: <0.20% (^1H NMR). The ^1H NMR spectrum was identical with that of the unlabeled species **18**, except for the missing signal for OCHB. The ^{13}C NMR spectrum was identical with that of **18**.

*4.8.2.2. Compound [1-D_1]**19**.* $[\alpha]_D^{20}$ +14.3 (*c* 0.56, acetone); H at boron bearing carbon atom: <0.20% (^1H NMR). The ^1H NMR spectrum was identical with that of the unlabeled species **19**, except for the missing signal for OCHB. The ^{13}C NMR spectrum was identical with that of **19**.

4.9. Reductive removal of carbamoyloxy group from boronates 18, 19, and [1-D_1]18

These reactions were performed with $LiAlD_4$ (1.2 equiv) or $LiBEt_3H$ (1.1 equiv) in Et_2O according to General Procedure A given in Ref. 5.

Boronate **18** (0.290 g, 0.511 mmol) was reduced with $LiAlD_4$ and yielded silylmethylboronate (1*R*)-[1-D_1]**5** (0.112 g, 57%); $[\alpha]_D^{20}$ +38.2 (*c* 0.9, acetone) {lit.[5] $[\alpha]_D^{20}$ +39.3 (*c* 2.0, acetone)} as a colorless oil. Similarly, boronate **19** (0.212 g, 0.373 mmol) gave silylmethylboronate (1*S*)-[1-D_1]**5** (0.069 g, 48%); $[\alpha]_D^{20}$ +38.1 (*c* 0.9, acetone). Boronate [1-D_1]**18** (0.899 g, 1.58 mmol) was reduced with $LiBEt_3D$ and gave silylmethylboronate (1*S*)-[1-D_1]**5** (0.482 g, 79%); $[\alpha]_D^{20}$ +38.5 (*c* 1.5, acetone) {lit.[5] $[\alpha]_D^{20}$ +38.7 (*c* 1.54, acetone)}.

Their ^1H and ^{13}C NMR spectra were identical with each other and with those for these compounds reported in the literature.[5]

4.10. Oxidative cleavage of B–C bond in boronates (1*R*)- and (1*S*)-[1-D_1]5

These reactions were performed with H_2O_2 in aqueous $NaHCO_3$/THF at 50 °C according to General Procedure B given in Ref. 5.

Boronate (1*R*)-[1-D_1]**5** (0.083 g, 0.215 mmol), derived from boronate **18**, yielded deuterated silylmethanol (*R*)-[1-D_1]**6** (0.033 g, 92%) as a colorless oil. Similarly, boronate (1*S*)-[1-D_1]**5** (0.067 g, 0.174 mmol), derived from boronate **19**, gave (*S*)-[1-D_1]**6** (0.025 g, 86%). Similarly, boronate (1*S*)-[1-D_1]**5**, derived from [1-D_1]**18**, was converted to (*S*)-[1-D_1]**6** (0.159 g, 79%; H<0.3%); $[\alpha]_D^{20}$ +0.57 (*c* 1.1, acetone). Their ^1H and ^{13}C NMR spectra were identical with each other and with those for these compounds reported in the literature.[5]

4.11. Esterification of deuterated silylmethanols (*R*)- and (*S*)-[1-D_1]6 to (*R*)-MTPA ester

Small samples (15–25 mg) of these alcohols were derivatized with (*S*)-MTPACl according to General Procedure C given in Ref. 5. The ^1H NMR spectrum (400.1 MHz, $CDCl_3$) of the (*R*)-MTPA ester of the deuterated silylmethanol derived from boronate **18** showed a significant resonance at 4.20 (t, *J*=1.0 Hz; ee 99%) indicating (*R*) configuration for the alcohol. The ^1H NMR spectra of the (*R*)-MTPA ester of the deuterated silylmethanols derived from boronates **19** and [1-D_1]**18** showed a significant resonance at 4.11 (t, *J*=1.0 Hz; ee 99%) indicating (*S*) configuration for the alcohols.

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