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Direct Chemical Synthesis of Chiral Methanol of 98% ee and Its Conversion to [$^2H_1$,^3H]Methyl Tosylate and [$^2H_1$,^3H-Methyl]Methionine

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Abstract: This paper describes the synthesis of chiral methanols [(*R*)- and (*S*)-CHDTOH] in a total of 12 steps starting from (chloromethyl)dimethylphenylsilane. The metalated carbamates derived from (dimethylphenylsilyl)methanol and secondary amines were borylated at low temperatures (−78 or −94 °C) using borates derived from *tert*-butyl alcohol and (+)-pinane-2,3-diol or (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol to give diastereomeric boronates (dr 1:1 to 5:1). The carbamoyloxy group could be replaced smoothly with inversion of configuration by an isotope of hydrogen using $LiAlH(D)_4$ [or $LiBEt_3H$(D,T)]. If the individual diastereomeric boronates were reduced with $LiAlD_4$ and oxidized with H_2O_2/$NaHCO_3$, monodeuterated (dimethylphenylsilyl)methanols of ee > 98% resulted. The absolute configurations of the boronates were based on a single-crystal X-ray structure analysis. Brook rearrangement of the enantiomers of (dimethylphenylsilyl)-[$^2H_1$,^3H]methanol prepared similarly furnished the chiral methanols which were isolated as 3,5-dinitrobenzoates in 81% and 90% yield, respectively. For determination of the enantiomeric excesses (98%), the methyl groups were transferred to the nitrogen of (*S*)-2-methylpiperidine and $^3H\{^1H\}$ NMR spectra were recorded. The Brook rearrangement is a stereospecific process following a retentive course. The chiral methanols were also transformed into methyl tosylates used to prepare [$^2H_1$,^3H-methyl]methionines in high overall yields (>80%).

Introduction

The chiral methyl group carrying one atom each of ^1H, ^2H, and ^3H has captured the imagination of chemists since the first syntheses of the enantiomers of chiral acetic acid and the determination of their configuration by Cornforth's[1] and Arigoni's[2] groups.[3,4] The chiral methyl group was used to analyze stereochemical problems in chemistry and biochemistry, particularly of methylations.[4,5] To do that the chiral acetate was converted to *N*,*N*-ditosylmethylamine and used to methylate L-homocysteine to give L-methionine with a chiral methyl group. Floss et al. demonstrated that the ee and absolute configuration of the chiral methyl group can also be determined by transfer to the nitrogen of chiral, nonracemic 2-methylpiperidine and use of ^3H NMR spectroscopy.[6] Recently, chiral *N*,*N*-ditosylmethylamine was prepared in a short synthesis directly, albeit of low ee (66%).[7]

We reasoned that chiral methanol would be the smallest and most versatile compound with a chiral methyl group so far not prepared directly, that is, without involving cleavage of a C−C bond. The chiral methyl tosylate would be a strong methylating agent, contrary to *N*,*N*-ditosylmethylamine used to methylate potassium 4-methoxybenzoate to prepare CHDTOH[8b] of low enantiomeric excess (ee 44−58%). Chiral methanol was formed during the degradation of natural products containing a chiral methoxy group. Arigoni's group obtained [$^2H_1$,^3H]methyl tosylate by thermal decomposition of *N*-[$^2H_1$,^3H]methyl-*N*-nitroso-*p*-toluenesulfonamide.[9]

Results and Discussion

We thought that the [1,2]-Brook rearrangement[10] could form the basis for the synthesis of chiral methanol. This 1,2-silyl

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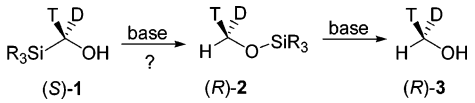
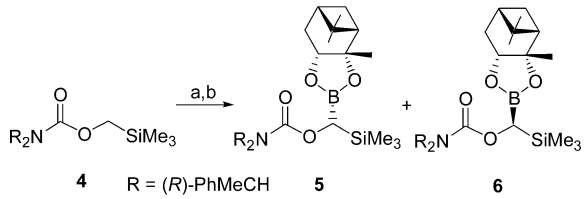
Scheme 1. [1,2]-Brook Rearrangement of a Labeled Silylmethanol



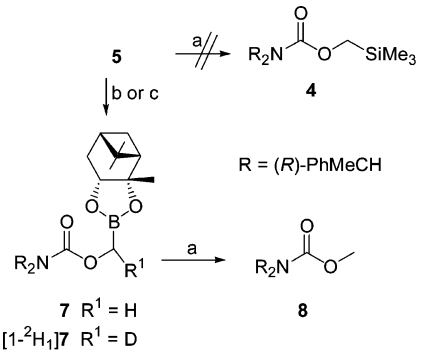
Scheme 2. Synthesis of Boronates from Carbamates[a]



[a] (a) *s*-BuLi/TMEDA/Et_2O, −78 °C; (b) mixed borate of (+)-pinane-2,3-diol and *tert*-butyl alcohol.

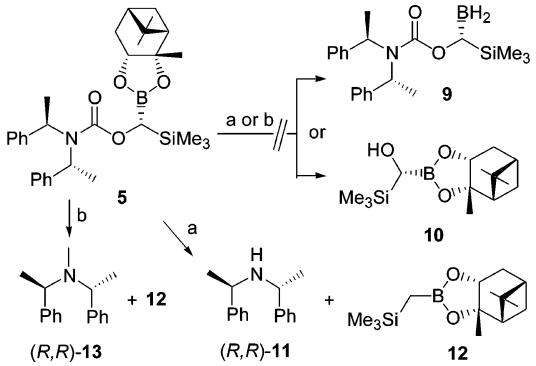
migration occurs with partial or complete inversion of configuration for secondary and tertiary α-silyl benzyl alcohols, respectively, but with retention (>97%) of configuration if the phenyl substituent is replaced by an alkyl group.[10−12] Thus, labeled silylmethanol **1** seemed to be a suitable precursor for the desired chiral methanol **3** (Scheme 1). Labeled silylmethanol (*S*)-**1** will give chiral methanol (*R*)-**3** if the silyl group is replaced by protium with retention of configuration. The stereochemical outcome of this transformation was open, as the intermediate carbanionic species would probably be less stable than that bearing an alkyl group. The synthesis of the enantiomers of **1** by enantioselective reduction of unstable formylsilanes[13,14] did not seem to be possible. Therefore, we developed a new method involving manipulation of a sp^3-hybridized carbon bearing a silyl group. Recently, boronates **5** and **6** were obtained by diastereoselective borylation[15] (dr up to 17:1 in favor of **5**) of metalated (trimethylsilyl)methyl carbamate **4** derived from (*R*,*R*)-bis(1-phenylethyl)amine with mixed borates containing (+)-pinane-2,3-diol (Scheme 2). The very stable *N*,*N*-diisopropylcarbamoyloxy group was tolerated in the first place as labile alternatives are known.[16] We envisaged transforming these compounds into the enantiomers of labeled (trimethylsilyl)-methanol and finally chiral methanol. Heating boronate **5** with propanoic acid in diglyme at 150 °C did not replace the B−C by a H−C bond as found for trialkylboranes[17] (Scheme 3). Hoping that **5** could first be desilylated and then deborylated to give a chiral methyl carbamates, in the isotopic series, **5** was treated with $Bu_4NF{\cdot}3H_2O$ and $Bu_4NF{\cdot}xD_2O$ in THF to furnish boronates **7** (73%) and [1-$^2H_1$]**7** (80%, 25% of **7**, 75% of a 1:1 mixture of monodeuterated diastereomers), respectively. The intermediate carbanion with a boron substituent is evidently configurationally labile and racemized prior to deuteriation/protonation.

Scheme 3. Replacing the B−C or Si−C Bond in Boronate **5** by H−C Bonds[a]



[a] (a) $EtCO_2H$, diglyme, 150 °C; (b) $Bu_4NF{\cdot}3H_2O$, THF, 50 °C (73%); (c) $Bu_4NF{\cdot}xD_2O$, THF, 50 °C (80%).

Scheme 4. Reduction of Boronate **5** with $LiAlH_4$[a]



[a] (a) $LiAlH_4$ (5.7 mol equiv)/Et_2O, 1 h reflux (**12**: 84%); (b) $LiAlH_4$ (7.4 mol equiv)/THF, 21 h reflux (**12**: 79%, (*R*,*R*)-**13**: 91%).

As it was not possible to replace the dioxyboryl group of boronate **5** at all or the silyl group stereospecifically by isotopes of hydrogen, we decided to reduce it to a monoalkylborane. This should then be transformed into a trialkylborane which would possibly give the desired carbamate without a boron substituent on exposure to propanoic acid at 150 °C. Thus, a mixture of **5** and excess $LiAlH_4$ was refluxed in diethyl ether for 1 h (Scheme 4). The crude product consisted of *N*,*N*-bis-(1-phenylethyl)amine (*R*,*R*)-**11** and a compound (84%) having, surprisingly, structure **12**. Similarly, diastereomer **6** was reduced to the same boronate in 74% yield. When boronate **5** was reduced with a large excess of $LiALH_4$ in refluxing THF for 21 h, (trimethylsilyl)methylboronate **12** and (*R*,*R*)-**13**, the *N*-methyl derivative of (*R*,*R*)-**11**, were obtained. It was found later that boronates were smoothly reduced already at 0 °C in 1 h with 1.05−1.1 mol equiv of $LiAlH_4$ or $LiBEt_3H$ in high yield. Surprisingly, boronate **5** was transformed into **12** in low yield by a large excess (15 mol equiv) of even $NaBH_4$ sluggishly in dry ethanol at ambient. We assume that the hydride ion is first transferred from the reducing agent to the boron[18] and from there to the neighboring carbon atom with concomitant substitution of the carbamoyloxy group under inversion of configuration. The reductive removal of the carbamoyloxy group was a marvelous discovery and eventually paved the way to chiral silylmethanol.

Silylmethylboronate **12**, which was quite stable, was oxidized slowly by $H_2O_2/NaHCO_3$ (Scheme 5). To circumvent isolation

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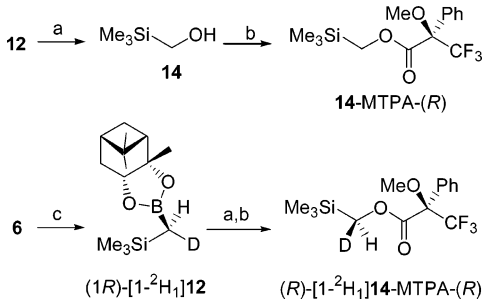
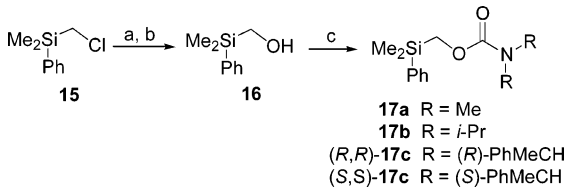
Scheme 5. Oxidation of (Trimethylsilyl)methylboronates and Preparation of Mosher Esters[a]



[a] (a) H_2O_2/$NaHCO_3$/H_2O/THF, ambient, 65 h; (b) (*S*)-MTPACl/pyridine (2 steps: 27%); (c) $LiAlD_4$ (5 mol equiv)/Et_2O, reflux (85%); (a,b) (15%).

Scheme 6. Synthesis of (Dimethylphenylsilyl)methanol and Its Carbamates[a]

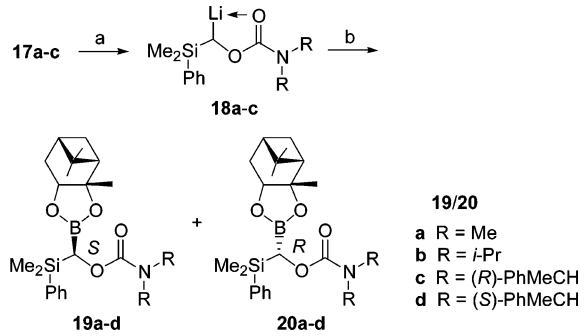


[a] (a) CH_3CO_2Na/NaI/DMF/reflux, 2 h; (b) $LiAlH_4/Et_2O$ (combined yield: 87%); (c) for **17a**: $Me_2NC(O)Cl/Et_2N$*i*-Pr/DMAP/toluene, reflux (83%); (c) for **17b**: *i*-$Pr_2NC(O)Cl/Et_2N$*i*-Pr/DMAP/toluene, reflux (86%); (c) for (*R*,*R*)-**17c**: (*R*,*R*)-$(PhMeCH)_2NH/COCl_2/Et_2N$*i*-Pr/toluene, 0 °C, then DMAP and **16**, reflux, 79%; (*S*,*S*)-**17c**: (*S*,*S*)-$(PhMeCH)_2NH/COCl_2/Et_2N$*i*-Pr/toluene, 0 °C, then DMAP and **16**, reflux, 63%.

of the volatile (trimethylsilyl)methanol[19] (bp 120−122 °C), the crude product was dissolved in CH_2Cl_2, dried, and treated with (*S*)-Mosher chloride [(*S*)-MTPACl]/pyridine. The ester[20] could be isolated easily but in low yield (27%). Similarly, boronate **6** was transformed into ester (*R*)-[1-$^2H_1$]**14**-MTPA-(*R*), except that $LiAlH_4$ was replaced by $LiAlD_4$. The low combined yield was mitigated by the high enantiomeric excess (>98%), reflecting the ee of (+)-pinane-2,3-diol (98−99% ee).[21] Oxidative cleavage of the B−C bond follows a mechanism with retention of configuration.[22] Therefore, replacement of the carbamoyloxy group has to occur stereospecifically with (very likely) inversion of configuration.

To lower the volatility of the silylmethanol we switched from the trimethylsilyl to the dimethylphenylsilyl group. (Dimethylphenylsilyl)methanol (**16,** bp 58 °C/0.1 mbar) was prepared in 87% overall yield from the commercially available chloromethylsilane **15** (Scheme 6).[15,23] To study the influence of the replacement of a methyl by a phenyl group on the diastereoselectivity of the borylation and find a pair of diastereomers which can be separated easily by flash chromatography, carbamates **17a**−**c** were prepared by esterification of (dimethylphenylsilyl)methanol (**16**) with four carbamoyl chlorides. The carbamates were borylated by the conditions optimized for the (trimethylsilyl)methyl carbamates (Scheme 7). They were deprotonated with *s*-BuLi/TMEDA in diethyl ether or THF at −78 °C in less than 5 min (with *n*-BuLi/TMEDA in 15 min). However, routinely 15 min were used with *s*-BuLi to generate

Scheme 7. Lithiation and Borylation of (Dimethylphenylsilyl)methyl Carbamates **17**[a]



[a] (a) *s*-BuLi/TMEDA/Et_2O/−78 °C, 15 min; (b) mixed borate of (+)-pinane-2,3-diol and *tert*-butyl alcohol; yields and ratios of diastereomers **19**/**20** in Table 1.

Table 1. Borylation of (Dimethylphenylsilyl)methyl Carbamates **17a**−**c** with the Mixed Borate Derived from (+)-Pinane-2,3-diol and *tert*-Butyl Alcohol

carbamate	temp.	boronates/ratio[a]	yield
17a	−78 °C	**19a**:**20a**/1.4:1	68%
17b	−78 °C	**19b**:**20b**/4:1	77%
17b	−95 °C	**19b**:**20b**/4.3:1	67%
(*R*,*R*)-**17c**	−78 °C	**19c**:**20c**/5:1	83%
(*R*,*R*)-**17c**	−95 °C	**19c**:**20c**/7:1	68%
(*S*,*S*)-**17c**	−78 °C	**19d**:**20d**/3:1	71%
(*S*,*S*)-**17c**	−95 °C	**19d**:**20d**/5:1	60%

[a] All reactions were performed in Et_2O using *s*-BuLi/TMEDA for metalation at −78 °C; the ratios were determined by ^1H NMR spectroscopy of the crude products.

lithiated carbamates **18a**−**c**, which were borylated with the mixed borate of *tert*-butyl alcohol and (+)-pinane-2,3-diol [(*S*)-pinane-2,3-diol] (Table 1). The configurations at the boron-bearing carbon atoms are already given here, but the determinations are dealt with later. Compared to boronates with the trimethylsilyl group, the differences in the polarities of **19**/**20** became smaller. Boronates **19a**−**c**/**20a**−**c** could be separated by flash chromatography with increasing difficulty. Separation of **19c**/**20c** by HPLC could be done easily, and homogeneous **19d** could be obtained only by HPLC. The ratio of diastereomers increased from 1.4:1 (R = Me) to 7:1 [R = (*R*)-PhMeCH]. The diastereoselectivity was higher for (*R*,*R*)-**17c** (**19c**/**20c** 5:1, matched pair) than for (*S*,*S*)-**17c** (**19d**/**20d** 3:1, mismatched pair). Lowering the reaction temperature for the borylation from −78 to −94 °C increased the diastereoselectivity marginally.

Finally, (*S*,*S*)-**17c** was borylated with the mixed borate **22** derived from (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol (**20**)[24,25] (Scheme 8). The use of this C_2-symmetric diol was inspired by the work of Hoffmann[25] and Matteson et al.,[26] who found that it is a superior director for syntheses with boronic acid esters. The lithiated carbamate **18c** [R = (*S*,*S*)-PhMeCH] furnished diastereomers **23**/**24** in a ratio of 1.2:1, which could be separated easily by flash chromatography (TLC: R_f = 0.40 and 0.24 for hexanes/EtOAc 10:1). The (*R*)-configuration at the boron-bearing carbon atom of the more polar and crystalline **24** was

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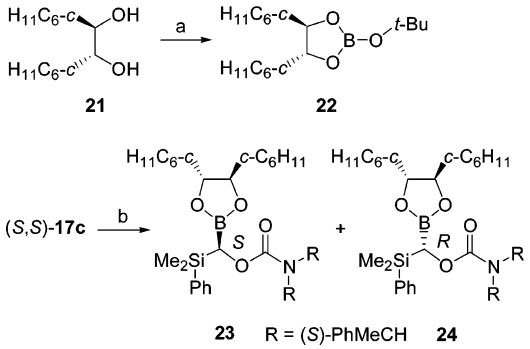
Scheme 8. Borylation of (*S*,*S*)-**17c** with a Mixed Borate of (*R*,*R*)-1,2-Dicyclohexylethane-1,2-diol[a]



[a] (a) (*t*-BuO)$_3$B/PhMe/heat (100%); (b) *s*-BuLi/TMEDA/Et$_2$O, −78 °C, 15 min, **22**, (**23**/**24** 1.2:1, 78%).

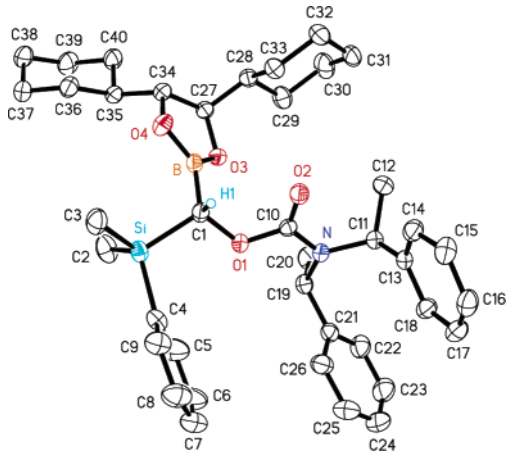
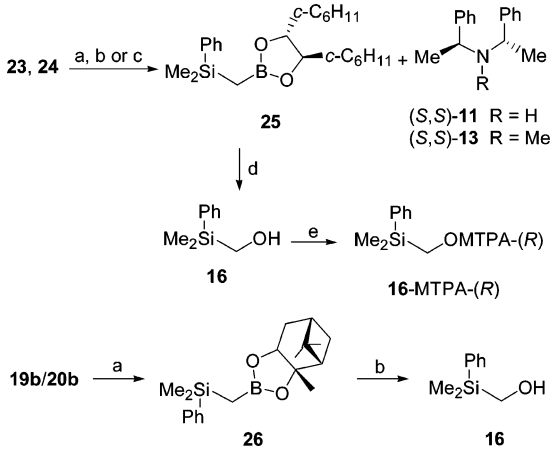


Figure 1. Molecular structure of **24** in the solid state (40% ellipsoids, all hydrogen atoms except H(1) omitted for clarity).

secured by a single-crystal X-ray structure analysis (Figure 1). Surprisingly, the diastereoselectivity is low.

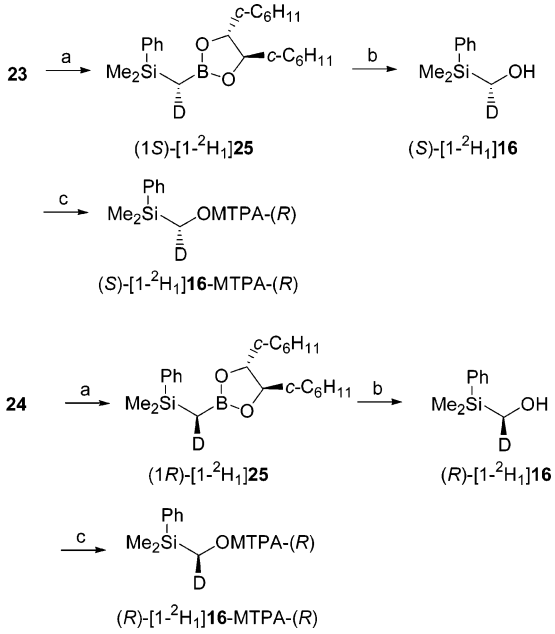
To determine the configurations of boronates **19** and **20** they were transformed into deuterated (dimethylphenylsilyl)methanols and compared as their Mosher esters to those obtained from boronates **23** and **24** of known configuration. Their optimized reduction could be performed with 1.1 mol equiv of LiAlH(D)$_4$ or LiBEt$_3$H(D) under very mild conditions (Et$_2$O, 0 °C, 30 min) (Scheme 9). If boronate **24** was reduced by a large excess of LiAlH$_4$ (5 mol equiv) in refluxing THF, the desired **25** was isolated in 71% yield along with 67% of (*S*,*S*)-**13** formed by reduction of the lithium carbamidate (see Scheme 4). Boronate **25** could be oxidized with H$_2$O$_2$/NaHCO$_3$ smoothly in 86% yield, which became the standard procedure for cleavage of the B−C bond. The workup was improved by stirring the reaction mixture with pentaerythritol to remove boric acid, and (dimethylphenylsilyl)methanol (**16**) was esterified with (*S*)-Mosher chloride/pyridine to give ester **16**-MTPA-(*R*) needed for comparison. Reduction−oxidation of a mixture of **19b**/**20b** worked as well as that of **23** and **24**. Reduction of the homogeneous boronates **23** and **24** with LiAlD$_4$ and oxidative cleavage of the B−C bonds known to occur with retention of configuration furnished silylmethanols (*S*)- and (*R*)-[1-^{2}H$_1$]**16** assuming inversion of configuration for the substitution process with the deuteride (Scheme 10). The SiCHD groups of the two diastereomeric Mosher esters of 99% de resonated as well-separated triplets in the ^{1}H NMR spectrum {400.13 MHz; (*S*)-[1-^{2}H$_1$]**16**-MTPA-(*R*): $\delta = 4.11$, $J = 1.5$ Hz; [(*R*)-[1-^{2}H$_1$]**16**-MTPA-(*R*): $\delta = 4.20$, $J = 1.5$ Hz}. Determination of the configurations of boronates derived from (+)-pinane-2,3-diol was performed similarly and is detailed in the Supporting Information.

Scheme 9. Conversion of Boronates **23** and **24** to Mosher Esters and of a Mixture of **19b**/**20b** to **16**[a]



[a] (a) **23**: LiAlH$_4$ (1.1 mol equiv/Et$_2$O)/0 °C, 30 min [71% of **25** along with 67% of (*S*,*S*)-**11**; 87% of **26**]; (b) **23** or **24**: LiBEt$_3$H (1.1 mol equiv/Et$_2$O)/0 °C, 30 min (93% for **23**, 81% for **24**); (c) **24**: LiAlH$_4$ (5 mol equiv/THF)/reflux, 21 h [62% of **25** along with 59% of (*S*,*S*)-**13**]; (d) H$_2$O$_2$/NaHCO$_3$/H$_2$O/THF, 50 °C, pentaerythritol (86% for **25**; 78% for **26**); (e) (*S*)-MTPACl/pyridine (90%).

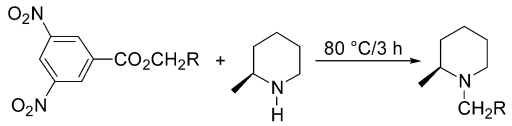
Scheme 10. Transformation of Boronates **23** and **24** into Deuteriated (Dimethylphenylsilyl)methanols and Determination of Their Enantiomeric Excesses[a]



[a] (a) LiAlD$_4$/Et$_2$O, 0 °C (95% for **23**; 91% for **24**), (b) H$_2$O$_2$/NaHCO$_3$/H$_2$O/THF, 50 °C (yield of (*S*)-[1-^{2}H$_1$]**16**: 88%; yields of (*R*)-[1-^{2}H$_1$]**16**: 79% for (*R*)-[1-^{2}H$_1$]**25** from **24**); (d) (*S*)-MTPACl/pyridine/CH$_2$Cl$_2$ (yields ≥90%).

In summary, lithiation of carbamates **17a**−**c** gave configurationally labile lithium-complexed carbanions which were kinetically resolved by the borates. The mixed borate of (+)-pinane-2,3-diol and *tert*-butyl alcohol preferentially induced the (*S*)-configuration at the boron-bearing carbon atom irrespective of the substituents at nitrogen. The low diastereoselectivity (1.2:1) for carbamate (*S*,*S*)-**17c** with borate **22** was very likely the

Scheme 11. Transfer of the Methyl Group from Methyl 3,5-Dinitrobenzoate to (*S*)-2-Methylpiperidine



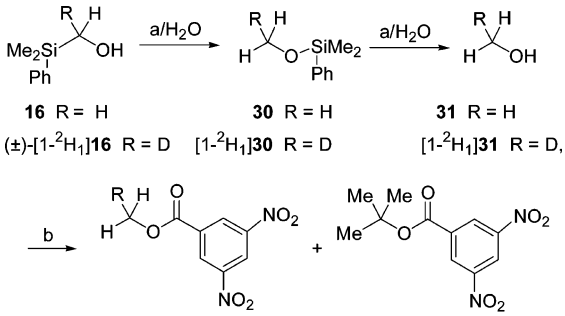
27 R = H [$^2H_1$-methyl]**27** R = D **28** **29** R = H [7-$^2H_1$]**29** R = D

result of opposing induction (mismatched case). Formation of virtually equal amounts of diastereomers **23** and **24** in the latter case is advantageous for the preparation of chiral methanols because both enantiomers are needed for complementary stereochemical investigations.

[1,2]-Brook Rearrangement of (Dimethylphenylsilyl)-methanol. Three challenges had to be overcome before the conversion of (*R*)- and (*S*)-[1-$^2H_1$,^{3}H]**16** to the chiral methanols could be addressed: (1) optimization of reaction conditions for the rearrangement of (dimethylphenylsilyl)methanol; (2) isolation of the formed methanol, possibly as a derivative; and (3) optimization of the conditions for determination of the enantiomeric excess of chiral methanol with unlabeled methanol. Floss and Anet et al. found that the ee of the chiral methyl group can be determined directly by ^{3}H NMR spectroscopy after transfer to the nitrogen of (*R*)- or (*S*)-2-methylpiperidine.[6] We envisaged preparing the 3,5-dinitrobenzoate of the chiral methanol in the reaction mixture, which would hopefully facilitate its isolation, and the subsequent transfer of the chiral methyl group to commercial (*S*)-2-methylpiperidine (ee 94%). To check whether the methyl group can be transferred, a deep red colored mixture of methyl 3,5-dinitrobenzoate (**27**, 10 mg) and (*S*)-2-methylpiperidine (**28**, 20 equiv) was heated under argon in an NMR tube at 80 °C for 6 h (Scheme 11). One-half of the reaction mixture was taken and diluted with CD_2Cl_2, and a ^{1}H NMR spectrum (400.13 MHz) was recorded. The ratio of **27**/**29**/MeOH was 5:69:26, satisfactory for determination of the ee of chiral methanol. Using the [$^2H_1$]methyl ester as electrophile, the ^{1}H NMR spectrum showed the expected AB system for the two diastereotopic protons of the CH_2D group.[27]

Kinetic studies revealed that the reaction rate for the Brook rearrangement was highest in DMSO and that considerable negative charge develops on the silicon-bearing carbon atom.[10a] To minimize possible partial racemization of the intermediate silyloxymethylanion, we effected the rearrangement of (dimethylphenylsilyl)methanol (**16**) in solvents containing water.[12] The [1,2]-Brook rearrangement of **16** was finished (TLC) in DMSO-d_6 containing D_2O (5%) and *t*-BuOK (50 mg/mL) after 3 h at ambient temperature (Scheme 12). The formed CH_2DOH could be detected by ^{1}H NMR spectroscopy. As the methanol could not be isolated from DMSO, which was also not compatible with 3,5-dinitrobenzoyl chloride, it was replaced by TMU (*N*,*N*,*N*′,*N*′-tetramethylurea) selected from a series of aprotic solvents (DMF, HMPTA, DMPU = 1,3-dimethyl-2-oxohexahydropyrimidine,TMU) tested. The best and reproducible results were obtained using TMU (2 mL) containing up to 0.5 mmol of (dimethylphenylsilyl)methanol, D_2O (0.12 mL, 6%), and *t*-BuOK (0.100 g) as base at room temperature (20−25 °C). After 16−18 h dry THF and excess pyridine and 3,5-dinitrobenzoy1 chloride were added, which furnished methyl (**27** or [1-$^2H_1$]-

Scheme 12. [1,2]-Brook Rearrangement of **16** and Isolation of Methanol as 3,5-Dinitrobenzoate[a]



16 R = H **30** R = H **31** R = H

(±)-[1-$^2H_1$]**16** R = D [1-$^2H_1$]**30** R = D [1-$^2H_1$]**31** R = D,

27 R = H **32**

[$^2H_1$-methyl]**27** R = D

[a] (a) *t*-BuOK/polar aprotic solvent/up to 6% of H_2O; 20−25 °C, 16−18 h, then (b) 3,5-$(O_2N)_2C_6H_3C(O)Cl$/pyridine, 50 °C, 1 h (for both steps: 75−90% of **27**).

27; combined yield: 75−90%) and *tert*-butyl 3,5-dinitrobenzoate (**32**). Monodeuterated (dimethylphenylsilyl)methanol yielded monodeuterated benzoate ($^2H_1$: 99%), indicating that no deuterium−hydrogen exchange took place under the strongly basic conditions.

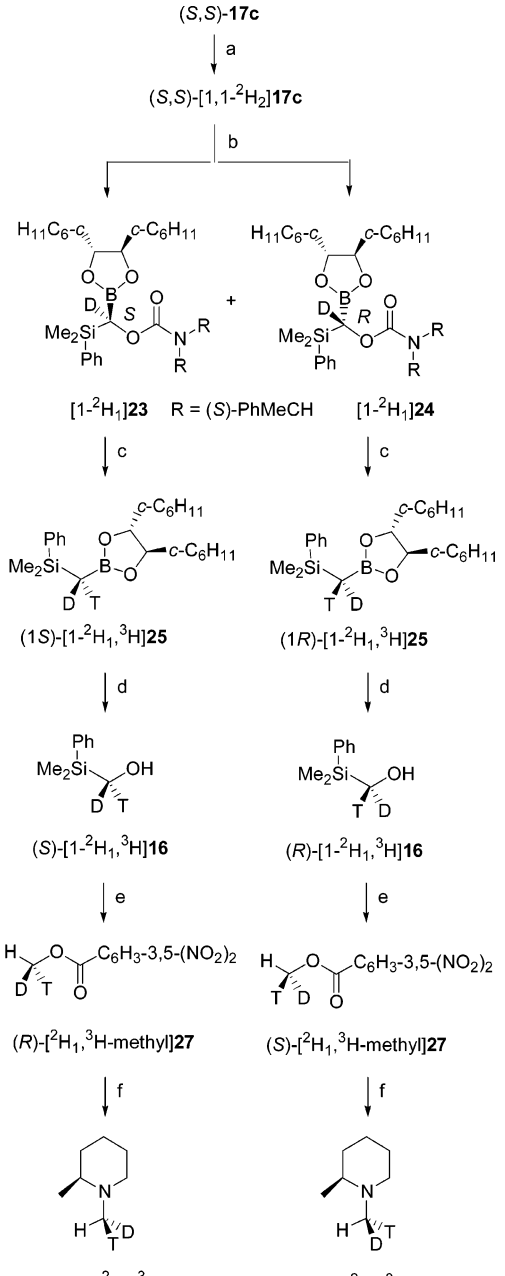
Preparation and Rearrangement of (*R*)- and (*S*)-(Dimethylphenylsilyl)-[1-$^2H_1$,^{3}H]methanol. As both enantiomers of chiral methanol were to be prepared, borylation of carbamate (*S*,*S*)-**17c** with borate **22** derived from (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol was used. To prepare chiral methanol of high specific activity the tritium should be introduced via $LiBEt_3T$.[28] To make sure that all molecules contain one deuterium atom, the dideuterated carbamate (*S*,*S*)-[1,1-$^2H_2$]**17c** was the appropriate precursor obtained from (*S*,*S*)-**17c** by four cycles of metalation and quenching with D_2O in 92% yield (**$^2H_2$** > 99% by ^{1}H NMR) (Scheme 13). The labeled carbamate was metalated and borylated with the mixed borate **22**. The two deuterated diastereomeric boronates formed in a ratio of 1.25:1 in favor of the less polar [1-$^2H_1$]**23** in a combined yield of 72%.

Each diastereomer was reduced with freshly prepared $LiBEt_3T$.[28] To complete the reduction excess $LiBEt_3H$ was added only to the reaction mixture containing [1-$^2H_1$]**23** after 20 min. Workup and purification furnished (1*S*)- and (1*R*)-[1-$^2H_1$,^{3}H]**25** in yields of 68% and 77% and of high specific activity, 11.3 (306.0 mCi)/mmol and 15.3 GBq (412.9 mCi)/mmol, respectively. The boronates (1*S*)- and (1*R*)-[1-$^2H_1$,^{3}H]-**24** were oxidized to silylmethanols (*S*)- and (*R*)-[1-$^2H_1$,^{3}H]**16** obtained in 60% and 90% yield, respectively. After appropriate dilution with unlabeled **16**, samples of both silylmethanols were rearranged to the chiral, nonracemic methanols isolated as their 3,5-dinitrobenzoates (*R*)- and (*S*)-[$^2H_1$,^{3}H-methyl]**27** in yields of 81% [3.87 GBq (104.7 mCi)/mmol] and 90% [3.83 GBq (103.6 mCi)/mmol], respectively.

A few milligrams of the benzoate (*R*)-[$^2H_1$,^{3}H-methyl]**27** were reacted with a large excess (20 equiv) of commercial (*S*)-2-methylpiperidine (ee 94%[29]) and heated to effect methylation at nitrogen. The cooled reaction mixture was diluted with CD_2Cl_2 before recording the $^3H\{^1H\}$ NMR spectrum (A, Figure 2). It shows that the *N*-[$^2H_1$,^{3}H]methyl-2-methylpiperidine was a

(27) Anet, F. A. L.; Kopelevich, M. *J. Am. Chem. Soc*. **1989**, *111*, 3429−3431.
(28) Andres, H.; Morimoto, H.; Williams, P. G. *J. Chem. Soc., Chem. Commun*. **1990**, 627−628.
(29) Doller, D.; Davies, R.; Chackalamannil, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1275−1278.

Scheme 13. Synthesis of Chiral Methanols and Determination of Their Enantiomeric Excess[a]



[a] (a) 4 × (TMEDA (1.2 equiv)/*s*-BuLi (1.15 equiv)/THF, −78 °C, 10 min; then D_2O in THF), 92%; (b) TMEDA (1.2 equiv)/*s*-BuLi (1.1 equiv)/THF, −78 °C, 15 min, then borate **22** (1.3 equiv), 3 h, 40% of [1-$^2H_1$]**23** and 32% of [1-$^2H_1$]**24**; (c) $LiBEt_3{}^3H$ (68% for [1-$^2H_1$]**23**, 77% for [1-$^2H_1$]**24**); (d) H_2O_2/THF/$NaHCO_3$ (60% for (1*S*)-[1-$^2H_1$,^3H]**25**, 90% for (1*R*)-[1-$^2H_1$,^3H]**25**); (e) *t*-BuOK/TMU/6% H_2O, ambient, 16−18 h, then 3,5-dinitrobenzoyl chloride/pyridine/THF (81% for (*S*)-[1-$^2H_1$,^3H]**16**, 90% for (*R*)-[1-$^2H_1$,^3H]**16**); (f) (*S*)-2-methylpiperidine.

diastereomeric mixture consisting mainly of the species with a (*S*)-configured chiral methyl group and an estimated 3−4% of the species with the (*R*)-configured one. Consequently, the ee of the chiral methyl benzoate was 92−94%, in agreement with the ee of (*S*)-2-methylpiperidine. (*S*)-2-Methylpiperidine of ≥99% ee obtained by resolution of the racemate[29] (see also Supporting Information) was reacted with (*S*)-[$^2H_1$,^3H-methyl]-**27** and a mixture of (*S*)- and (*R*)-[$^2H_1$,^3H-methyl]**27** in a ratio of 2:1, respectively. The segments of the $^3H\{^1H\}$ NMR spectra

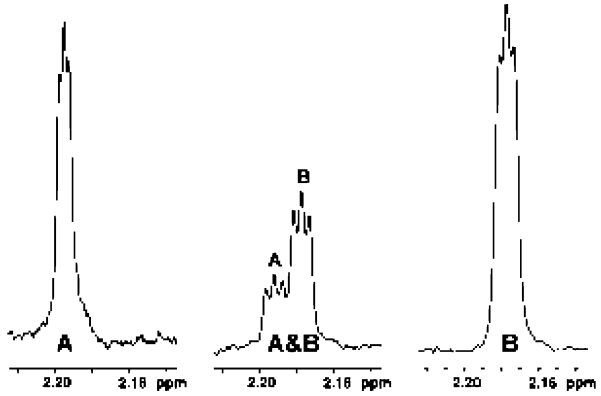
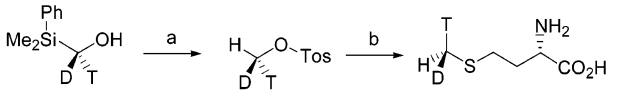


Figure 2. Segments of the $^3H\{^1H\}$ NMR spectra recorded at 426.79 MHz of reaction mixtures after heating (80 °C) for 6 h in a thick-walled NMR tube under argon, cooling, diluting with CD_2Cl_2, and sealing; (A) (*R*)-[$^2H_1$,^3H-methyl]**27** (6 mg) and commercial (*S*)-(+)-2-methylpiperidine (0.063 mL, ee 94%, chemical purity 97%); (A and B) mixture of (*R*)-[$^2H_1$,^3H-methyl]**27** (2.2 mg), (*S*)-[$^2H_1$,^3H-methyl]**27** (4.2 mg), and (*S*)-(+)-2-methylpiperidine (0.067 mL prepared by resolution, ee ≥ 99%); (B) (*S*)-[$^2H_1$,^3H-methyl]**27** (6 mg) and (*S*)-(+)-2-methylpiperidine (0.063 mL, ee ≥ 99%).

Scheme 14. Synthesis of Chiral Methyl Tosylate and Its Use To Methylate L-Homocysteine[a]



[a] (a) *t*-BuOK/TMU/6% H_2O, ambient, 16−18 h, then pyridine/THF/*t*-BuOK/*p*-toluenesulfonyl chloride (−50 °C), aqueous work up, 91% of (*R*)-**30** [94% of (*S*)-**30**]; (b) *S*-benzyl L-homocysteine/liquid NH_3/Na; EtOH, then (*R*)-**30**, 0 °C; 88% of [$^2H_1$,^3H-methyl-(*S*)]**31**{96% of [$^2H_1$,^3H-methyl-(*R*)]**31**}.

of the methyl resonances are given in Figure 2 (B and A,B, respectively). The reaction mixture of the benzoate (*S*)-[$^2H_1$,^3H-methyl]**27** is stereochemically homogeneous (98% ee).

Anet and Floss et al. reported that the tritium of (7*R*)-[7-$^2H_1$,^3H]**29** resonates at higher field than that of (7*S*)-[7-$^2H_1$,^3H]-**29**.[6] The latter was obtained by the sequence given in Scheme 13 from [1-$^2H_1$]**23** having an (*S*)-configuration at C-1. Consequently, the intermediate chiral methanol was (*R*)-configured, as an (*S*)-configured chiral methyl group resulted on methylation of the nitrogen atom. Complementary results were obtained with the chiral methanol derived from [1-$^2H_1$]**24**. These findings coincide with the assumption that substitution of the carbamoyloxy group by hydride (deuteride or tritide) occurred with inversion of configuration. Furthermore, this finding is unequivocal proof of the microscopic configurational stability of the intermediate "silyloxymethylanion" of the Brook rearrangement occurring with retention[10−12] of configuration.

Preparation of Methyl Tosylate and L-Methionine with Chiral Methyl Groups. Methyl 3,5-dinitrobenzoate is an excellent derivative of chiral methanol for isolation but a weak alkylating agent. After quite a while we found the appropriate conditions to convert the chiral methanol formed in the reaction mixture to the corresponding tosylate, which is a highly reactive methyl donor superior to *N*,*N*-ditosylmethylamine (Scheme 14). We demonstrated that the sodium salt of the homocysteine[4] was alkylated with chiral methyl tosylate to give L-methionine with a chiral methyl group, which is the standard substrate for feeding experiments to study methyl transfer in biosynthetic pathways.[4] Furthermore, the chiral methyl tosylate transferred its methyl

group to (*S*)-2-methylpiperidine at room temperature in a smooth reaction (^{3}H NMR, 98% ee). Methionine with the (*R*)-configured methyl group was prepared similarly. The combined yields for both steps were >80%.

Conclusion

We have shown that metalated carbamates of (dimethylphenylsilyl)methanol are configurationally labile and kinetically resolved by borates derived from chiral, nonracemic diols. The diastereomeric boronates are reduced stereospecifically with complex hydrides by substitution of the carbamoyloxy group with inversion of configuration by an isotope of hydrogen. This extraordinary transformation enabled the preparation of the homochiral (dimethylphenylsilyl)-[^{2}H$_1$,^{3}H]methanols, which were subjected to Brook rearrangement to furnish both enantiomers of chiral methanol of ee 98% in a total of only 12 steps. The methanols were also converted to chiral methyl tosylates used to prepare L-methionines with chiral methyl groups. Further work will focus on the use of these samples of methionine to elucidate the methyl transfer in the biosynthesis of fosfomycin.

Acknowledgment. This work was supported by grant no. P14985-N03 from the Fonds zur Förderung der wissenschaftlichen Forschung. We are grateful to S. Felsinger and C. Tyl for recording the NMR spectra, S. Schneider for the separation of boronate mixtures by preparative HPLC, and Dr. L. Brecker for help with the interpretation of NMR spectra.

Supporting Information Available: All experimental procedures and spectroscopic data; X-ray crystallographic data of **24** in PDF as well as CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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