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A Convenient Procedure for the Reduction of S-(+)-Silyl Serine Methyl Ester to Chiral Serinol Derivatives.

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Abstract: *The reduction of S-(+)-serine methyl ester silyl ether with $NaBH_4$ followed by acidic workup produced the chiral serinol derivatives with minimum racemization. Addition of MeMgBr gave the functionalized amine diol in high yield with no racemization.*

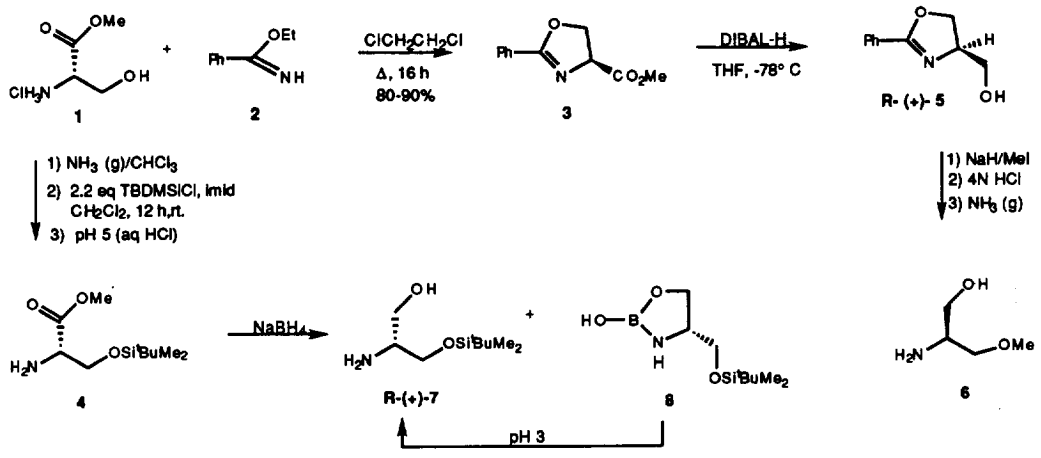
Chiral amino alcohols are some of the most commonly employed fragments from the "chiral pool" to serve as mediators for asymmetric induction in auxiliary based methodologies.[1a-e] Reduction of amino acids by using any one of a number of procedures provides the chiral amino alcohols in a direct and efficient manner.[2a-i] However, serine presents a special problem in that direct reduction would result in the achiral amino diol. As a result, serine generally requires the protection of all functionality prior to reduction.[3]

Serine derived chiral oxazolines have become important for some of our research endeavors. Consequently, we have recently described a procedure for preparing the chiral serinol derivative **6** via reduction of the serine ester oxazoline **3** obtained from S-(+)-serine methyl ester hydrochloride **1** and the phenyl imidate **2** (Scheme 1).[4] The process requires seven steps overall from commercially available starting materials to yield the desired derivative **6** in 40-50% overall yield. While the desired chiral amino alcohol was obtained, the procedure is somewhat laborious and indirect. Furthermore, the enantiomeric purity of the intermediate hydroxymethyl oxazoline **R-(+)-5** has been found to vary due to racemization during the reduction. This has been determined by chiral HPLC comparison with the racemic mixture prepared in an analogous fashion.[5]

We now report a simplified and much more efficient procedure for preparing the chiral, nonracemic silyl derivative **(R)-7** (Scheme 1) in moderate to excellent yield.

This paper is dedicated to Harry H. Wasserman in honor of his 75th birthday.

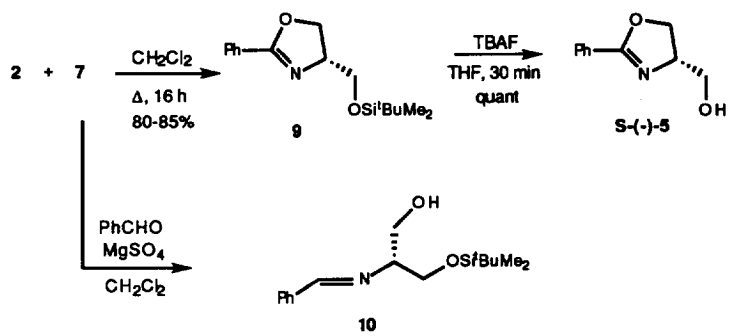
Scheme 1



Serine methyl ester hydrochloride[6] was liberated to the free amine and treated with 2.1 equiv TBDMSCl and 2.1 equiv imidazole to furnish the corresponding silyl ether **4** in 95-99% purified yield following slightly acidic aqueous workup.[7] This transformation has been carried out successfully on up to 25 grams of the serine methyl ester.

The silyl ether **4** was reduced using 4 equiv of $NaBH_4$ in MeOH or EtOH at 35 °C to yield mixtures of the amino alcohol **(R)-7** and the boronate ester **8**. The latter was hydrolyzed to the free amino alcohol **(R)-7** using phosphate buffer (pH 3).[8] The boronate ester **8** was the exclusive product (80-85% following chromatography) when the reduction was performed in THF. Racemization of **(R)-7** is minimized under the acidic conditions used for hydrolysis, although observed to some extent presumably due to silyl group migration.

A number of workup conditions for the hydrolysis of the boronate ester **8** were examined and the use of the conditions described above generally give reproducible yields with only slight variation in enantiomeric purity. Repetition of the reaction conditions described produced ratios of 99:1, 97:3, 96:4 and 94:6, as determined by chiral HPLC analysis of the oxazoline **S-(-)-5** prepared from **(R)-7**.[9]

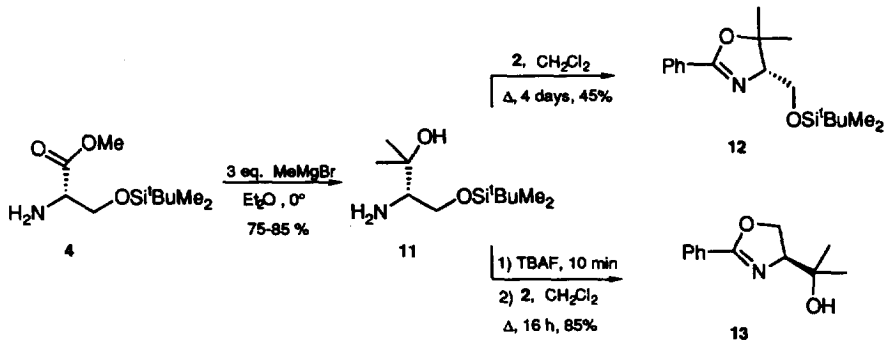


The enantiomeric purity of **(R)-7** may also be determined by comparison of the corresponding Mosher esters[10] of the imine **10** derived from benzaldehyde.

The absolute configuration of the oxazoline **S-(-)-5** is opposite to that obtained by the direct reduction of the L- serine methyl ester oxazoline **3** which gave R-(+)-5.[4] The silyl amino alcohol **(R)-7** may be stored as a matrix in benzene at -20 °C. Silyl group migration was found to be minimized under these storage conditions for up to 2 weeks as determined by chiral HPLC analysis of the corresponding oxazoline **S-(-)-5**.[11]

In order to access an amino alcohol derivative that would not be prone to racemization due to silyl group migration, the silyl amino ester **4** was treated with MeMgBr furnishing the tertiary alcohol **11** in 75-85% yield after chromatography. This material may be utilized to form the corresponding chiral oxazolines **12** or **13** in either absolute configuration at C-4 using the conditions outlined in Scheme 2.

Scheme 2



The tertiary alcohol **13** obtained in this fashion was found to be enantiomerically pure by chiral HPLC comparison with the racemic mixture. This material was spectroscopically identical to the alcohol obtained by treatment of the oxazoline **3** with excess MeMgBr.

There was a notable advantage in using the 3° alcohol **11** since no racemization was observed during the Grignard addition and silyl group migration was no longer a concern.[12] On the other hand, the hydride reduction processes (e.g. **3** → **5**) invariably resulted in partial racemization.

We are currently assessing the utility of the dimethyl derivative **11** in chiral oxazoline mediated asymmetric processes.[4,13] These results will be reported in due course.

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7. Experimental procedure: S-(+)-serine methyl ester, 10 g (84 mM), was dissolved in 100 mL CH_2Cl_2 and t-butyldimethylsilyl chloride (2.1 equiv,176 mm, 27 g) was added. The mixture was cooled to 0 °C and 2.1 equiv (176 mM, 12 g) of imidazole was added portionwise over 5 min. The bath was removed and the mixture stirred 12-16 h at 25 °C. The mixture was poured into 50 mL H_2O (pH 5, HCl). The layers were separated and the organic layer washed 2x with 25 ml H_2O, dried over Na_2SO_4, filtered and concentrated. Vacuum distillation using a 15 cm column (b.p. 112-114 at 3 Torr) gave 16.5 g (96%) of the silyl serine methyl ester, **4** $[\alpha]_D$ = +7.0 (c 2.1, $CHCl_3$); ^1H ($CDCl_3$): δ 0.00-0.02 (d, J = 3.5, 6H), 0.84 (s, 9H) 1.8 (br s, 1H) 3.5 (t, J = 4.2, 1H) 3.7 (s, 3H) 3.7-3.9 (dd, J = 3.7, J = 4.5, 2H); ^{13}C ($CDCl_3$) -6.2, -5.8, 17.93, 25.48, 51.64, 55.26, 65.16, 174.24.
8. Typical experimental procedure: The silyl serine methyl ester (1.5 g, 6.4 mM) was dissolved in 25 mL MeOH and 4 equiv of $NaBH_4$ (25.6 mM, 974 mg) were added at once. The mixture was warmed to 35 °C and the reduction was complete after 1 h as indicated by TLC. At completion, the mixture was treated with pH 3 phosphate buffer and hydrolysis monitored by TLC. The mixture was concentrated and the silyl amino alcohol was extracted with $CHCl_3$. The organic layer was concentrated to dryness and the amino alcohol (R)-7 was eluted through a plug of silica gel (5 x 4 cm) using MeOH. $[\alpha]_D$ = 2.1 (c 1.6, $CHCl_3$); ^1H ($CDCl_3$) 0.00 (s, 6H), 0.83 (s, 9H) 2.55 (br s, 1H) 2.88 (p, J = 5.25, 1H), 3.39-3.58 (m, 4H); ^{13}C ($CDCl_3$) -5.53, 18.14, 25.78, 53.97, 63.95, 65.61. The yields were somewhat variable (due to incomplete hydrolysis of the boronate ester) but generally better than 75%. The resultant material was used to form the oxazoline from the imidate using standard protocol.[9] The enantiomeric purity was determined by chiral HPLC[5] of the hydroxymethyl oxazoline **5**, to be 93-95%.
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