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Efficient Synthesis of a Configurationally Stable L-Serinal Derivative

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Abstract: An efficient synthesis of a configurationally stable L-serinal derivative **8** was achieved using an *N*-hydroxymethyl group in about 50% overall yield in four steps from L-serine. Not more than 1% racemization was observed during the preparation of **8**. Its enantiomeric integrity was maintained for at least 15 days at room temperature, and it was stable on silica gel. The orthogonal protective groups of **8** would make it a useful chiral synthon.

α-Amino aldehydes are useful compounds in asymmetric synthesis and widely used as either chiral synthons or chiral auxiliaries.[1] *N*-Protected serinal, among others, has been of particular importance because it has served as a key starting material for the synthesis of many biologically important molecules such as sphingosine,[2a] hydroxy-L-glutamic acid,[2b] kainic acid,[2c] destomic acid,[2d] and hydroxyleucine.[2e] In addition, the hydroxyl group in serinal can be utilized for further transformation.[3] However, α-amino aldehydes have been well-known to be both chemically and configurationally labile because of the rather acidic proton positioned α to the carbonyl group.[1a,4] Among the configurationally stable serinals **1**−**4** reported to date (Figure 1),[5] the popular Garner aldehyde (**1**) and Reetz serinal (**2**) have been reported to be problematic in a few cases.[6] We report herein an efficient preparation of another configurationally and chemically stable L-serinal derivative with an *N*-hydroxymethyl group and a study of its stability under different conditions. We have shown previously that attachment of the *N*-hydroxymethyl group to *N*-Boc-L-phenylalaninal enhanced greatly its configurational stability.[7] Particularly, the enduring stability over two weeks at room temperature was notable. The *N*-hydroxymethyl group used to enhance the stability has also been utilized for the stereoselective introduction of the *β*-hydroxyl group of (−)-statine.[8]

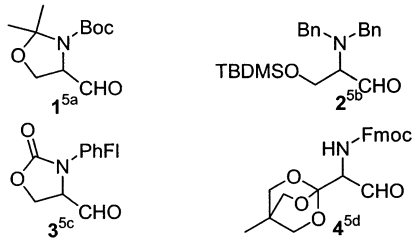
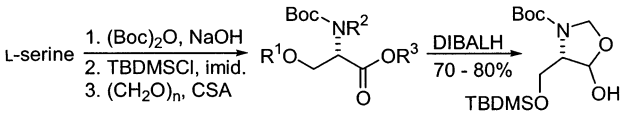


FIGURE 1. Known configurationally stable serinals in the literature.

SCHEME 1. Synthesis of the L-Serinal Derivative 8



5 $R^1=R^2=R^3=H$; 95%
6 R^1=TBDMS, $R^2=R^3=H$; 85%
7 R^1=TBDMS, R^2,$R^3=CH_2$; 80%

First, *N*-Boc-L-serine (**5**) was prepared from L-serine (> 97% ee) under basic conditions, although it is commercially available (Scheme 1). Orthogonal protection of the hydroxyl group was done with TBDMSCl in DMF to give a better yield of **6**.[9] The *N*-hydroxymethyl group of oxazolidinone **7** was introduced by heating **6** with paraformaldehyde in the presence of a catalytic amount of (±)-10-camphorsulfonic acid (CSA).[10] The yield in the two-step sequence was 68%. The use of *p*-toluenesulfonic acid (*p*-TsOH) in place of (±)-CSA as an acid catalyst reduced the yield of **7** by about 15%, probably because of the more facile deprotection of the Boc or TBDMS group with *p*-TsOH.

The reduction reaction of **7** with DIBALH in CH_2Cl_2 or toluene gave **8** in 70−80% yield. Slow addition of DIBALH was essential for obtaining good yields of **8** on a multigram scale. Production of the overreduced diol **9** (see Scheme 2) was significant with large-scale reactions, and some of the starting compound was also recovered. Both **7** and **9** could be easily separated from **8** with silica gel chromatography. Thus, the desired L-serinal derivative **8** was obtained in about 50% overall yield from L-serine according to the four-step reaction scheme (Scheme 1).

The reduction of several oxazolidinones similar to **7** in structure was claimed to give better results with $NaBH_4$ in MeOH or $Li(O^tBu)_3AlH$ in THF.[11] The reduction

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SCHEME 2. Transformation of 7, 8, and 14 into the Mosher Ester Derivative 13

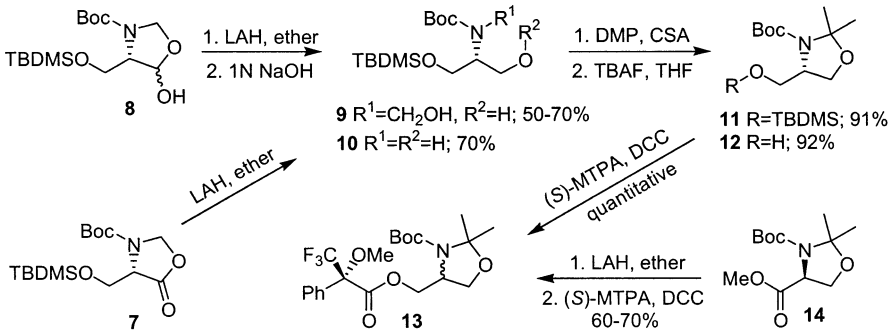

TABLE 1. HPLC Assay of the Mosher Ester 13 from the Different Sources

no.	starting compound	dr [(*S*,*R*)-**13**:(*S*,*S*)-**13**] (% de)
1	**8**	90.6:1 (97.8)
2	**7**	133:1 (98.5)
3	**14**	1:162 (98.8)

TABLE 2. Storage Test of the L-Serinal Derivative 8

no.	temp (°C)	time (days)	dr [(*S*,*R*)-**13**:(*S*,*S*)-**13**] (% de)
1	−22	30	85.5:1 (97.7)
2	2	15	90.6:1 (97.8)
3	2	30	89.3:1 (97.8)
4	rt	15	88.5:1 (97.8)
5	rt	30	40.0:1 (95.1)

TABLE 3. Stability Test of the L-Serinal Derivative 8 under Harsh Conditions

no.	conditions	time (h)	dr [(*S*,*R*)-**13**:(*S*,*S*)-**13**] (% de)
1	SiO_2/rt	3	97.7:1 (98.0)
2	TEA/rt	3	50.6:1 (96.1)
3	reflux	3	82.8:1 (97.6)
4	SiO_2/reflux	3	66.8:1 (97.1)
5	TEA/reflux	3	30.4:1 (93.6)

reaction with $Li(O^tBu)_3AlH$ gave results similar to those with DIBALH on a small scale. However, the $NaBH_4$ reduction gave mostly a methyl ester derivative of **6** with the *N*-hydroxymethyl group (R^1 = TBDMS, R^2 = CH_2-OH, R^3 = Me in Scheme 1) in our hands that was derived from the opening of the lactone ring with MeOH.

Next, pure **8** obtained after chromatographic separation was converted into the Mosher ester derivative **13** to check the possibility of racemization during the DIBALH reduction and the following purification (Scheme 2). The *N*-hydroxymethyl group (R^1) of **9** produced from the LAH reduction of **8** was removed with 1 N aqueous NaOH in MeOH in good yield to give **10**. Efficient protection of **10** with 2,2-dimethoxypropane (DMP) in the presence of (±)-CSA gave **11**, and desilylation of **11** with tetrabutylammonium fluoride (TBAF) hydrate resulted in **12** in excellent yield. It appears that no significant migration of the TBDMS group takes place during the formation of **9**, **10**, or **11** unlike the report in the literature.[6d]

The free hydroxyl group of **12** was then coupled with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) to give (*S*,*R*)-**13** in the presence of DCC and a catalytic amount of DMAP in quantitative yield.[5a,12] Its diastereomeric purity is shown in Table 1. The diastereomeric purities of other Mosher esters, (*S*,*R*)-**13** and (*S*,*S*)-**13** derived from **7** and **14**, respectively (see Scheme 2), are also given for comparison. Note here that the known ester **14** is prepared from L-serine[5a,13] and it is in an enantiomeric relationship with **12**. Careful HPLC analysis of **13** prepared from **8** indicated that not more than 1% racemization occurred during the preparation of pure **8** (entry 1). The loss of enantiomeric purity seems to be originated mainly from the DIBALH reduction and the following purification steps.[7] A ca. 0.3% decrease in the diastereomeric purity was observed with the Mosher ester produced from **7** when compared to that produced from **14** (Table 1, entry 2 vs entry 3).

Finally, the configurational stability of **8** was tested under different conditions, and the results are shown in Tables 2 and 3. In the storage test, **8** obtained after storage for a certain period at different temperatures was converted to **13** by applying the same protocol as shown in Scheme 2 (Table 2). It is evident that the L-serinal derivative **8** is quite stable both chemically and configurationally at low temperature and shows no racemization even at room temperature for at least 15 days (entry 4). However, significant racemization was detected after a month at room temperature (entry 5).

The stability test under harsh conditions was undertaken by either stirring at room temperature or heating a solution of **8** in THF under reflux in the presence of silica gel or triethylamine (TEA) for 3 h (Table 3). The same method used for the storage test was employed for the assay of the enantiomeric purities. At room temperature, it was quite stable with silica gel (entry 1) but showed about 2% erosion in enantiomeric excess with base, TEA (entry 2). Its enantiomeric purity remained practically the same even after refluxing for 3 h in THF without SiO_2 or TEA (entry 3). The presence of SiO_2 in refluxing THF resulted in a little racemization (entry 4). The racemization was significant with TEA at the refluxing temperature of THF (entry 5). The chemical stability, however, was sufficiently robust to tolerate all of the harsh conditions, and no significant decomposition was observed for any sample. We have also tried to utilize commercially available *N*-Boc-*O*-benzyl-L-serine as a starting material for the other serinal derivative. How-

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ever, the *N*-Boc-*O*-benzyl-L-serinal derivative with the *N*-hydroxymethyl group, similar in structure to **8**, was not so stable, and about 3−4% racemization was realized after the DIBALH reduction and the purification steps (not shown). The reason the *N*-Boc-*O*-benzyl-L-serinal derivative is less stable than **8** is not clear at the present time.

In conclusion, an efficient synthesis of the configurationally stable L-serinal derivative **8** was achieved in about 50% yield in four steps from L-serine, and its configurational stability was firmly established by the HPLC analysis of its Mosher ester derivatives. A serinal derivative of 98% ee could be easily produced, starting from L-serine of >99% ee according to the present scheme. Its stability on silica gel would facilitate its purification with column chromatography, which is often desirable in the synthesis of complex natural products. Its durable stability would add more flexibility in synthetic design, too. In addition, use of the L-serinal derivative of high enantiomeric purity will enhance diastereoselectivity in reactions with other chiral reagents.[6b] The orthogonal protective groups on **8** would make it a versatile chiral synthon as well. The reactivity and stability of the aldehyde group in its hemiacetal form of **8** have been demonstrated in previous reports.[7,8]

Experimental Section

General Methods. Materials were obtained from commercial suppliers and were used without further purification. Methylene chloride was distilled from calcium hydride immediately prior to use. Likewise, THF, benzene, ether, and toluene were distilled from sodium benzophenone ketyl. DMF was dried with molecular sieves (4 Å). Air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere using oven-dried glassware and the standard syringe/septa technique. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm) followed by visualization with a molybdenum stain solution. Column chromatography was performed on silica gel 60 (70−230 mesh). Optical rotations were determined at ambient temperature with a digital polarimeter and are the average of five measurements. ^{1}H NMR spectra were measured at 300 MHz in $CDCl_3$ unless stated otherwise, and data were reported as follows in parts per million (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in hertz.). HPLC analyses were done with a μPorasil silica column.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-serine (5).** To an ice-cold solution of L-serine (0.54 g, 5.14 mmol) in a mixture of water (12 mL), *t*-BuOH (12 mL), and NaOH (0.23 g, 5.65 mmol) was added di-*tert*-butyl dicarbonate (1.23 g, 5.65 mmol) with stirring. After 1 h at 0 °C, the mixture was warmed to room temperature and stirred for 10 h. The mixture was concentrated to half its original volume with vacuum evaporation, and the resulting concentrate was extracted with pentane. The aqueous phase was acidified to pH 1−2 by slow addition of cold 1 N $KHSO_4$. The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the crude product as a colorless oil. Crystallization in hexane/Et_2O afforded **5** (1.00 g, 95%) as a white solid: mp 90 °C (dec.); R_f = 0.7 (8:1:1 BuOH/H_2O/AcOH); ^{1}H NMR δ 1.45 (s, 9H), 3.86 (d, 1H, J = 10.5), 4.06 (d, 1H, J = 10.5), 4.34 (br s, 1H), 5.69 (br s, 1H); ^{13}C NMR δ 28.3, 55.5, 62.9, 80.6, 156.2, 174.0. Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83. Found: C, 46.64; H, 7.32; N, 6.76.

***O*-(*t*-Butyldimethylsilyl)-*N*-(1,1-dimethylethoxy)carbonyl-L-serine (6).** To an ice-cold solution of **5** (1.00 g, 4.90 mmol) in DMF (10 mL) were added TBDMSCl (0.96 g, 6.30 mmol) and imidazole (1.00 g, 14.6 mmol) with stirring under a nitrogen atmosphere. After 1 h at 0 °C, the mixture was warmed to room temperature and stirred for 10 h. The reaction mixture was partitioned between Et_2O (2 × 25 mL) and 1 N aqueous HCl (20 mL), and the phases were separated. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography eluting with 4:1 hexane/EtOAc to give **6** (1.32 g, 85%) as a colorless oil: R_f = 0.6 (9:1 CH_2Cl_2/MeOH); $[\alpha]^{26}_D$ +20.1 (*c* 0.63, $CHCl_3$); ^{1}H NMR δ 0.08 (s, 6H), 0.89 (s, 9H), 1.46 (s, 9H), 3.80 (dd, 1H, J = 9.9 and 5.0), 4.10 (dd, 1H, J = 9.9 and 3.3), 4.35 (m, 1H), 5.36 (d, 1H, J = 7.7); ^{13}C NMR δ −5.6 (two peaks), 18.2, 25.7, 28.3, 55.4, 63.5, 80.1, 155.6, 175.8. Anal. Calcd for $C_{14}H_{29}NO_5Si$: C, 52.63; H, 9.15; N, 4.38. Found: C, 52.35; H, 9.36; N, 4.27.

(4*S*)-4-[(*t*-Butyldimethylsilyloxy)methyl]-3-[(1,1-dimethylethoxy)carbonyl]-5-oxazolidinone (7). To a solution of **6** (1.32 g, 4.1 mmol) in toluene (40 mL) were added paraformaldehyde (1.09 g, 34.1 mmol) and (±)-10-camphorsulfonic acid (CSA, 0.113 g, 0.487 mmol). The reaction mixture was heated under reflux for about 25 min with azeotropic removal of water. The reaction mixture was cooled and washed with 1 N aqueous $NaHCO_3$ (40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was done with silica gel column chromatography (8:1 hexane/EtOAc) to give **7** (1.10 g, 80%) as a colorless oil: R_f = 0.6 (2:1 hexane/EtOAc); $[\alpha]^{26}_D$ +121.4 (*c* 0.85, $CHCl_3$); IR (KBr) 1800, 1700 cm^{-1}; ^{1}H NMR (DMSO, 100 °C) δ 0.01 (s, 6H), 0.82 (s, 9H), 1.42 (s, 9H), 3.88 (d, 1H, J = 10.5), 4.04 (d, 1H, J = 10.5), 4.22 (br s, 1H), 5.03 (d, 1H, J = 3.8), 5.36 (d, 1H, J = 3.8); ^{13}C NMR δ −5.8, −5.7, 18.0, 25.6, 28.2, 57.7, 61.8, 78.9, 81.7, 151.5, 171.6; MS (CI) 332 ([M + 1]$^+$, 54), 276 (47), 260 (26), 232 (100), 174 (31), 57 (58); HRMS (CI) calcd for $C_{15}H_{30}NO_5Si$ 332.1893 ([M + 1]$^+$), found 332.1902. Anal. Calcd for $C_{15}H_{29}NO_5Si$: C, 54.35; H, 8.82; N, 4.23. Found: C, 54.61; H, 8.80; N, 4.12.

***O*-*t*-Butyldimethylsilyl-*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-hydroxymethyl-L-serinal (8).** To a stirred solution of **7** (0.75 g, 2.26 mmol) in dry CH_2Cl_2 (35 mL) at −78 °C was added dropwise a 1.0 M solution of DIBALH in CH_2Cl_2 (2.49 mL, 2.49 mmol) under a nitrogen atmosphere, and the resulting mixture was stirred for 30 min. The rate of addition was adjusted so as to keep the internal temperature below −75 °C. The reaction was quenched by slowly adding cold MeOH (10 mL). Cold 1 N aqueous HCl solution (20 mL) was added to the resulting white emulsion, and the aqueous layer was then extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed with silica gel column chromatography (16:1 hexane/EtOAc) to give a diastereomeric mixture of **8** (0.56 g, 75%) as a white solid: R_f = 0.5 (2:1 hexane/EtOAc); IR (KBr) 3400, 1680 cm^{-1}; ^{1}H NMR (DMSO, 100 °C) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.44 (s, 9H), 3.50 (dd, 1H, J = 7.9 and 9.5), 3.58 (dd, 1H, J = 7.9 and 3.3), 3.72 (dd, 1H, J = 9.0 and 3.3), 4.73 (d, 1H, J = 3.3), 4.93 (d, 1H, J = 3.3), 5.36 (d, 1H, J = 4.4), 6.45 (d, 1H, J = 5.1); ^{13}C NMR (a mixture of diastereomers) δ −5.8, −5.5, 17.9, 18.1, 25.6, 25.8, 28.3, 28.4, 61.3, 63.3, 78.1, 80.5, 80.8, 98.9, 152.6; MS (CI) 334 ([M + 1]$^+$, 8), 278 (38), 248 (17), 216 (100), 57 (52); HRMS (CI) calcd for $C_{15}H_{32}NO_5Si$ 334.2050, found 334.2058. Anal. Calcd for $C_{15}H_{31}NO_5Si$: C, 54.02; H, 9.37; N, 4.20. Found: C, 54.18; H, 9.52; N, 4.16.

Procedure for Large-Scale Preparation of 8 by DIBALH reduction of Lactone 7. To a stirred solution of **7** (5.52 g, 16.7 mmol) in dry CH_2Cl_2 (167 mL) at −78 °C was added dropwise a 1 M solution of DIBALH in CH_2Cl_2 (26.6 mL, 26.6 mmol) under a nitrogen atmosphere with a syringe pump. The addition rate was 30 mL/h, and the total reaction time was 1 h. The reaction was quenched with the sequential slow addition of cold MeOH (25 mL) and water (13 mL). After warming to room temperature, the reaction mixture was stirred for 1 h (a white gel was formed). After dilution with EtOAc (100 mL) and $MgSO_4$, the resulting mixture was stirred for 1 h to facilitate filtration. The mixture was filtered and concentrated under reduced pressure. Purification was performed with silica gel column chromatography (16:1 hexane/EtOAc) to give a diastereomeric mixture of **8** (4.08 g, 74%) as a white solid. The overreduced product diol **9** was obtained in 10% yield (0.56 g), and the starting material **7** was recovered in 7% yield (0.38 g).

***O*-*t*-Butyldimethylsilyl-*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-hydroxymethyl-L-serinol (9).** To an ice-cold suspension of $LiAlH_4$ (37.8 mg, 1.00 mmol) in ether (3 mL) was added dropwise a solution of **7** or **8** (150 mg, 0.45 mmol) in ether (2 mL) under a nitrogen atmosphere. After the mixture was stirred for 20 min at 0 °C, the reaction was quenched with 1 N aqueous NaOH (1.5 mL). After $MgSO_4$ was added, the reaction mixture was stirred for 10 min. The resulting mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2:1 hexane/EtOAc) to give pure diol **9** (106 mg, 70%) as a colorless oil. The yield of this step was consistently between 50 and 70%: R_f = 0.25 (2:1 hexane/EtOAc); $[\alpha]^{26}_D$ +20.4 (*c* 0.6, $CHCl_3$); IR (KBr) 3419, 1698, 1682 cm^{-1}; ^1H NMR δ 0.07 (s, 6H), 0.89 (s, 9H), 1.49 (s, 9H), 1.70 (br s, 1H), 3.17 (br s, 1H), 3.60−4.10 (m, 5H), 4.20−5.20 (m, 2H); ^{13}C NMR (a mixture of two conformational isomers) δ −5.7 (two peaks), 18.1, 25.7, 28.2, 59.6, 61.3, 61.7, 61.8, 68.3, 69.7, 80.3, 80.5, 80.8, 80.9, 155.4, 156.1; MS (CI) 336 ($[M + 1]^+$, 4), 318 (77), 262 (94), 218 (100), 160 (32), 57 (48); HRMS (CI) calcd for $C_{15}H_{34}NO_5Si$ 336.2207, found 336.2209. Anal. Calcd for $C_{15}H_{33}NO_5Si$: C, 53.70; H, 9.91; N, 4.17. Found: C, 53.55; H, 10.08; N, 4.11.

***O*-*t*-Butyldimethylsilyl-*N*-[(1,1-dimethylethoxy)carbonyl]-L-serinol (10).** To a solution of **9** (75.3 mg, 0.22 mmol) in MeOH (5 mL) was added 1 N aqueous NaOH solution (1 mL). After the mixture was stirred for 1 h at room temperature, MeOH was evaporated. The residue was partitioned between water (2 × 50 mL) and EtOAc (2 × 50 mL), and the phases were separated. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (4:1 hexane/EtOAc) to give pure **10** (48 mg, 70%) as a colorless oil: R_f = 0.45 (2:1 hexane/EtOAc); $[\alpha]^{26}_D$ +17.2 (*c* 0.75, $CHCl_3$); IR (KBr) 3449, 3360, 1714, 1694 cm^{-1}; ^1H NMR δ 0.07 (s, 6H), 0.89 (s, 9H), 1.44 (s, 9H), 2.87 (br s, 1H), 3.50−3.90 (m, 5H), 5.15 (br s, 1H); ^{13}C NMR δ −5.6, 18.1, 25.8, 28.3, 52.6, 64.0, 64.1, 79.5, 156.0; MS (CI) 306 ($[M + 1]^+$, 53), 250 (93), 234 (58), 206 (100), 192 (54), 57 (53); HRMS (CI) calcd for $C_{14}H_{32}NO_4Si$ 306.2101, found 306.2098. Anal. Calcd for $C_{14}H_{31}NO_4Si$: C, 55.04; H, 10.23; N, 4.59. Found: C, 55.42; H, 10.31; N, 4.65.

(4*S*)-4-[(*t*-Butyldimethylsilyloxy)methyl]-2,2-dimethyl-3-[(1,1-dimethylethoxy)carbonyl]oxazolidine (11). To a solution of **10** (47.6 mg, 0.156 mmol) in benzene (25 mL) were added 2,2-dimethoxypropane (DMP, 211 mg, 2.03 mmol) and (±)-CSA (0.4 mg, 0.01 equiv). The mixture was heated under reflux for 30 min. After the mixture was concentrated, the same protection procedure was repeated to complete the reaction as described above for another 20 min. The resulting mixture was partitioned between water (2 × 50 mL) and Et_2O (2 × 50 mL), and the phases were separated. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20:1 hexane/EtOAc) to give **11** (49 mg, 91%) as a colorless oil: R_f = 0.75 (2:1 hexane/EtOAc); $[\alpha]^{30}_D$ +33.1 (*c* 0.7, $CHCl_3$; IR (KBr) 1703 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.89 (s, 9H), 1.47 (s, 9H), 1.39−1.54 (m, 6H), 3.39 (m, 1H), 3.68 (m, 2H), 3.76−4.10 (m, 2H); ^{13}C NMR (a mixture of two conformational isomers) δ −5.3, 18.2, 23.1, 24.6, 25.9, 26.7, 27.4, 28.4, 28.6, 58.4, 58.6, 61.4, 62.2, 64.9, 65.1, 79.7, 80.1, 93.4, 93.9, 151.9, 152.3; MS (CI) 346 ($[M + 1]^+$, 100), 246 (95), 232 (46); HRMS (CI) calcd for $C_{17}H_{36}NO_4Si$ 346.2395, found 346.2404. Anal. Calcd for $C_{17}H_{35}NO_4Si$: C, 59.09; H, 10.21; N, 4.05. Found: C, 59.44; H, 10.26; N, 4.20.

(4*R*)-2,2-Dimethyl-3-[(1,1-dimethylethoxy)carbonyl]-4-hydroxymethyloxazolidine (12). To a solution of **11** (51.5 mg, 0.149 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (TBAF·$3H_2O$, 56.4 mg, 0.179 mmol). After 30 min, the resulting mixture was partitioned between H_2O (2 × 50 mL) and EtOAc (2 × 50 mL), and the phases were separated. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2:1 hexane/EtOAc) to give **12** (31.7 mg, 92%) as a colorless oil: R_f = 0.5 (2:1 hexane/EtOAc); $[\alpha]^{30}_D$ +24 (*c* 0.46, $CHCl_3$); IR (KBr) 3458, 1698 cm^{-1}; ^1H NMR δ 1.50 (s, 9H), 1.55−1.69 (br s, 6H), 3.50−4.20 (m, 5H); ^{13}C NMR δ 24.6, 27.1, 28.4, 59.5, 65.2, 65.3, 81.1, 94.1, 154.2.

(*S*)-(−)-MTPA Ester of (4*R*)-2,2-Dimethyl-3-[(1,1-dimethylethoxy)carbonyl]-4-hydroxymethyloxazolidine [(*S*,*R*)-13]. To a solution of **12** (30 mg, 0.13 mol), DMAP (1.6 mg, 0.01 mmol), and MTPA (36.4 mg, 0.16 mmol) in dry CH_2Cl_2 (3 mL) was added a solution of DCC (53.5 mg, 0.26 mmol) in CH_2Cl_2 (2 mL). After the mixture was stirred at ambient temperature for 5 h, the resulting white suspension was filtered to remove *N*,*N*′-dicyclohexylurea. The residue was purified by silica gel column chromatography (9:1 hexane/EtOAc) to give quantitatively (−)-MTPA ester (*S*,*R*)-**13** as a colorless oil: R_f = 0.6 (2:1 hexane/EtOAc); IR (KBr) 1754, 1703 cm^{-1}; ^1H NMR (C_6D_6, 75 °C) δ 1.40 (br s, 12H), 1.54 (br s, 3H), 3.36 (s, 3H), 3.49 (dd, 1H, *J* = 9.3 and 5.9), 3.62 (dd, 1H, *J* = 9.3 and 2.0), 3.88 (m, 1H), 4.06 (m, 1H), 4.57 (dd, 1H, *J* = 10.3 and 3.4), 7.00−7.40 (m, 4H), 7.60 (br d, 1H, *J* = 7.3); ^{13}C NMR (a mixture of two conformational isomers) δ 23.0, 24.3, 26.6, 27.2, 28.3, 55.1, 55.2, 55.4, 64.1, 64.3, 64.8, 65.1, 80.5, 80.8, 84.7 (q, *J* = 29.7), 93.8, 94.1, 123.2 (q, *J* = 288), 127.3, 128.5, 129.7 (two peaks), 132.0, 151.4, 152.1, 166.1, 166.2. Anal. Calcd for $C_{21}H_{28}F_3NO_6$: C, 56.37; H, 6.31; N, 3.13. Found: C, 56.05; H, 6.42; N, 3.13.

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