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Preparation and Synthetic Applications of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals: Asymmetric Synthesis of (*S*)- and (*R*)-2-Amino-2-methylbutanoic Acids (Iva)[†]

Alberto Avenoza,*[‡] Carlos Cativiela,*[§] Francisco Corzana,[‡] Jesús M. Peregrina,[‡] and
María M. Zurbano[‡]

Departamento de Química (Química Orgánica), Universidad de La Rioja, 26001 Logroño, Spain, and
Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón,
Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain

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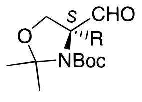
This report describes an efficient and convenient large-scale synthesis procedure for (*S*)- and (*R*)-*N*-Boc-α-methylserinal acetonides (**3** and **4**) starting from (*R*)-2-methylglycidol **5**. The application of both of these compounds as valuable chiral building blocks in the asymmetric synthesis of α-methylamino acids is also demonstrated by the synthesis of (*S*)- and (*R*)-isovalines (Iva) (**6** and **7**).

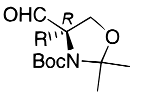
Introduction

In recent years, there has been a growing interest in chiral *N*-protected α-amino aldehydes because of their wide utility in organic synthesis.[1] In particular, (*S*)-*N*-Boc-*N*,*O*-isopropylidene serinal (**1**), known as Garner's aldehyde,[2] and its enantiomer **2** are of special interest, owing to their ready availability from natural sources (L-serine) and their pronounced versatility in stereocontrolled organic synthesis as chiral building blocks.[3] Recently, several studies on the synthesis of these aldehydes have been reported[4] since the development of a convenient large-scale procedure is crucial to their broad use in synthesis.

As a part of our research project on the asymmetric synthesis of α-amino acids, we have exploited the behavior of L-serinal **1** as a chiral starting material to synthesize bis(α-amino acids),[5] and we have also described two straightforward synthetic routes for the preparation of enantiomerically pure D-serinal **2** starting from naturally occurring L-serine.[6] In this context, and taking into account the special role that α-alkylamino acids[7] have played in the design of peptides with enhanced properties,[8] we have focused our attention on the stereoselective synthesis of α-methylamino acids. Indeed, one of us has recently published[9] the synthesis of the homologue of serinal **1**, the (*S*)-α-methyl derivative **3**, which can be regarded as an ideal precursor for the synthesis of α-methylamino acids. The synthesis of (*S*)-α-methylserinal **3** was achieved on a milligram scale starting from (*S*)-α-methylserine by using a procedure similar to that described for the synthesis of Garner's aldehyde.[2,4]



1: R = H
3: R = Me



2: R = H
4: R = Me

In this paper, we now describe a new and more convenient synthesis procedure for (*S*)-α-methylserinal **3** on a gram scale, starting from commercially available

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[†] Dedicated to Professor José Elguero on the occasion of his 65th birthday.

[‡] Universidad de La Rioja.

[§] Universidad de Zaragoza.

(1) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164.

(2) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (b) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18−27.

(3) For an extensive list on asymmetric reactions with L-serinal **1**, see: (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354−362. (b) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395−4398. (c) Kahne, D.; Yang, D.; Lee, M. D. *Tetrahedron Lett.* **1990**, *31*, 21−22. (d) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439−1446. (e) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370−4382. (f) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697−1700. (g) Boyd, E. C.; Paton, R. M. *Tetrahedron Lett.* **1993**, *34*, 3169−3172. (h) Blake, A. J.; Boyd, E. C.; Gould, R. O.; Paton, R. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2841−2847. (i) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257−1258. (j) Lee, C. S.; Forsyth, C. J. *Tetrahedron Lett.* **1996**, *37*, 6449−6452. (k) Hanessian, S.; Wang, W.; Gai, Y. *Tetrahedron Lett.* **1996**, *37*, 7477−7480. (l) Kauppinen, P. M.; Koskinen, A. M. P. *Tetrahedron Lett.* **1997**, *38*, 3103−3106. (m) Mordini, A.; Valacchi, M.; Nardi, C.; Bindi, S.; Poli, G.; Reginato, G. *J. Org. Chem.* **1997**, *62*, 8557−8559. (n) Deng, L.; Schärer, O. D.; Verdine, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 7865−7866. (o) Hertweck, C.; Goerls, H.; Boland, W. *Chem. Commun.* **1998**, 1955−1956. (p) Villard, R.; Fotiadu, F.; Buono, G. *Tetrahedron: Asymmetry* **1998**, *9*, 607−611. (q) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657−10670. For an extensive list on asymmetric reactions with D-serinal **2**, see: (a) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855−5858. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979−2984. (c) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C.-G.; Boulanger, T.; Norberg, B.; Evrard, G.; Durant, F. *J. Org. Chem.* **1991**, *56*, 5729−5733. (d) Raghavan, S.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Tetrahedron Lett.* **1993**, *34*, 5765−5768. (e) Kan, T.; Ohfune, Y. *Tetrahedron Lett.* **1995**, *36*, 943−946. (f) Han, B. H.; Kim, Y. C.; Park, M. K.; Park, J. H.; Go, H. J.; Yang, H. O.; Suh, D.-Y.; Kang, Y.-H. *Heterocycles* **1995**, *41*, 1909−1914. (g) Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Rocca, V. *Tetrahedron* **1995**, *51*, 8121−8134. (h) D'Aniello, F.; Falorni, M.; Mann, A.; Taddei, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1217−1226. (i) Garner, P.; Yoo, J. U.; Sarabu, R.; Kennedy, V. O.; Youngs, W. J. *Tetrahedron* **1998**, *54*, 9303−9316.

(4) (a) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31−32. (b) Meffre, P.; Durand, P.; Branquet, E.; le Goffic, F. *Synth. Commun.* **1994**, *24*, 2147−2152. (c) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673−11694. (d) Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527−529. (e) Ravi Kumar, J. S.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 6779−6782.

(5) (a) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1555−1558. (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 863−871.

(6) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Synthesis* **1997**, 1146−1150.

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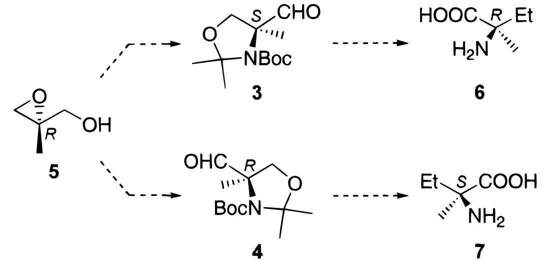
Scheme 1



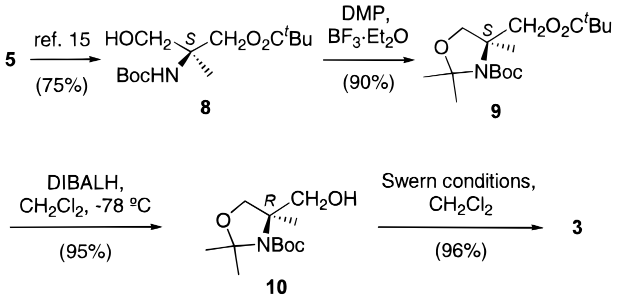
(*R*)-2-methylglycidol (**5**). Moreover, we report the synthesis, also starting from the same compound **5**, of the enantiomer of (*S*)-α-methylserinal **3**, (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal (**4**). Furthermore, we demonstrate the synthetic utility of both compounds (**3** and **4**) as chiral building blocks by carrying out the synthesis of both (*S*)- and (*R*)-2-amino-2-methylbutanoic acids (**6** and **7**) (Iva) (Scheme 1).

We selected (*S*)- and (*R*)-isovaline to prove the applicability of this method for the synthesis of the α-methylamino acids because of the significance that L- and D-Iva have attained in the past few years.[10] For example, a large number of studies have focused on these amino acids, particularly on D-Iva (also denoted by the letter code J), which is an important nonstandard constituent of a family of polypeptides known as peptaibols.[11] Peptaibols generally exhibit antimicrobial activity and are referred to as antibiotic peptides. The antimicrobial activity of the peptaibols is thought to arise from their ability to form helical ion channels in lipid membranes. The channels so formed are able to conduct ionic species, leading to the loss of osmotic balance and cell death. After searching in The Peptaibol Database[12] for query J, we found 67 peptides that incorporate the Iva residue.[13]

Results and Discussion

(*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal (3). Because the reported preparation[9] of **3** uses five steps and gives only 33% yield from (*S*)-α-methylserine, which is not commercially available, and because **3** was obtained only on a milligram scale, a better synthesis was clearly needed if it were to be the starting material for a practical synthesis of α-methylamino acids.

Scheme 2



As shown in Scheme 2, the new synthesis starts with commercially available (*R*)-2-methylglycidol (**5**) of 94% ee,[14] which was transformed into the corresponding compound **8** according to the protocol described in the literature.[15] Et_2AlCl-catalyzed cyclization of the trichloroacetimidate derivative of **5**, followed by pivaloylation, acid hydrolysis of the oxazoline ring, and further *tert*-butoxycarbonylation, gave alcohol **8** and an overall yield of 75% from **5**. After recrystallization from hexane, compound **8** was converted into oxazolidine **9** by the use of 2,2-dimethoxypropane (DMP) in acetone at room temperature with boron trifluoride etherate as catalyst.[4a,6,16] The cleavage of the pivaloate ester in compound **9** was achieved in good yield by reduction with DIBAL-H[17] to give alcohol **10**. This product was pure enough for use in the next step (94% ee[14]); it was therefore oxidized under Swern conditions[6,18] to obtain the required (*S*)-α-methylserinal **3**. In this way, building block **3** was prepared on a gram scale and in three steps with an overall yield of 82% from alcohol **8** (or in seven steps with a 61% yield from commercially available glycidol **5**) (Scheme 2).

(*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal (4). With the aim of obtaining large amounts of **4**, the building block enantiomer of **3**, to produce the opposite configuration of the reaction products derived from its synthetic application (α-methylamino acids, for example), we developed a straightforward and stereodivergent synthetic route from compound **5**. The same glycidol **5** was used as the source of chirality, because its enantiomer is not commercially available. Glycidol **5** was again transformed into compound **8**, but the hydroxyl group of this compound was now protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl) (1.3 equiv) using dichloromethane as solvent, to give compound **11** in a 60% yield, as shown in Scheme 3. To improve the synthetic method by attempting to increase the yield, DMF was used instead of dichloromethane and an excess of 2 equiv of silylating agent was added; an 85% yield was achieved.

In this case, the cleavage of the pivaloate ester in compound **11** was achieved only in 71% yield by reduction

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(7) (a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748. (b) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225−227. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599.

(8) (a) Mossel, E.; Formaggio, F.; Toniolo, C.; Crisma, M.; Boesten, W. H. J.; Broxterman, Q. B.; Kamphuis, J.; Quaedflieg, P. J.; Temussi, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1305−1314 and references therein. (b) Bellier, B.; McCort-Tranchenpain, I.; Ducos, B.; Danascimento, S.; Meudal, H.; Noble, F.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 3947−3956.

(9) Alías, M.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Lapeña, Y. *Tetrahedron* **1998**, *54*, 14963−14974.

(10) (a) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1445−1448. (b) Formaggio, F.; Crisma, M.; Bonora, G. M.; Pantano, M.; Valle, G.; Toniolo, C.; Aubry, A.; Bayeul, D.; Kampuis, J. *Pept. Res.* **1995**, *8*, 6−15. (c) Jaun, B.; Tanaka, M.; Seiler, P.; Kühnle, F. N. M.; Braun, C.; Seebach, D. *Liebigs Ann.* **1997**, 1697−1710.

(11) Jung, G.; Brückner, H.; Schmitt, H. In *Structure and Activity of Natural Peptides*; Voelter, W., Weitzel de Gruyter, G., Eds.; Berlin, 1981; p 75.

(12) The Peptaibol Database. A World Wide Web resource currently found at http://www.cryst.bbk.ac.uk/peptaibol/welcome.html; Whitmore L., Snook C. F., Wallace B. A., 1997

(13) (a) Rebuffat, S.; Goulard, C.; Bodo, B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1849−1855 and references therein. (b) Chikanishi, T.; Hasumi, K.; Harada, T.; Kawasaki, N.; Endo, A. *J. Antibiot.* **1997**, *50*, 105−110.

(14) Determined by ^{1}H or ^{19}F NMR (300 MHz) analysis of the corresponding (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetates.

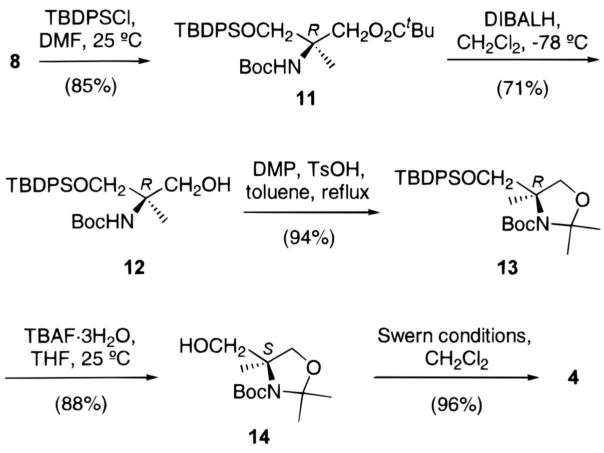
(15) Hatekayama, S.; Matsumoto, H.; Fukuyama, H.; Makugi, Y.; Irie, H. *J. Org. Chem.* **1997**, *62*, 2275−2279.

(16) Moriwake, T.; Hamano, S. I.; Saito, S.; Torii, S. *Chem. Lett.* **1987**, 2085−2088.

(17) (a) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453−461. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991. (c) Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: Stuttgart, 1994.

(18) (a) Tidwell, T. T. *Synthesis* **1990**, 857−870. (b) Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798−806.

Scheme 3



with DIBAL-H[17] to give alcohol **12**. Once again, to increase this yield we examined the basic hydrolysis of the ester group. However, because the cleavage of this function requires strong basic reagents (0.25 N NaOH, 12 h, rt or K_2CO_3/MeOH, 12 h, rt), which were incompatible with the other protecting group (TBDPS), we obtained the corresponding symmetric diol as the sole product.

Starting from compound **12**, the acetonide formation in compound **13** occurred without hydrolysis of the O−Si bond in the same conditions as described above for compound **9** but now only in a 63% yield. However, when the acetonide formation was carried out using DMP in toluene as a solvent with *p*-toluenesulfonic acid (TsOH) as a catalyst, at reflux, we obtained **13** in a 94% yield. This compound was desilylated by treatment with tetrabutylammonium fluoride (TBAF·$3H_2O$) to give alcohol **14** in 88% yield, because the use of other recent procedures to cleave silyl ethers was unsuccessful. In this sense, attempts to desilylate **13** under acidic conditions ($Sc(OTf)_3$; H_2O, MeCN)[19] failed.

Finally, the oxidation of alcohol **14** under Swern conditions[6,18] was completed to give the required building block (*R*)-α-methylserinal acetonide **4** in 96% yield (48% overall yield from alcohol **8**, using five steps).

Synthesis of (*R*)- and (*S*)-Isovaline. Starting from (*S*)-α-methylserinal **3** and (*R*)-α-methylserinal **4** and using five steps, we obtained both enantiomers of Iva with an excellent overall yield (61%) (Scheme 4).

Although Wittig methylenation of α-amino aldehydes has been reported to be problematic because racemization occurs during the reaction,[4a,16,20] in our case, this fact did not represent a problem because **3** and **4** are quaternary amino aldehydes. We therefore investigated two olefination methods. The first of these was based on the use of the zinc/methylene iodide/trimethylaluminum reagent, which gave optically pure material **15** in 80% yield. The second method proved to be more effective; the olefination was carried out under salt-free Wittig conditions using methyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide (KHMDS) as base, providing olefin **15** in 93% yield. Hydrogenation of this compound was completed in 12 h using palladium on carbon as a catalyst and ethyl acetate as a solvent at room temperature to give oxazolidine **16**.

Starting from this compound, our initial plan was to obtain the corresponding α-methylamino acid **6** in one step by trying Jones oxidation[20] because we thought that under the acid conditions of this reaction (sulfuric acid) cleavage of the acetonide moiety and hydrolysis of the *N*-Boc would take place. Unfortunately, after 6 h at room temperature no reaction was observed. As an alternative, we chose first to cleave the acetonide of **16** by Lewis acid hydrolysis, employing TsOH, but once again the reaction did not progress. When boron trifluoride−acetic acid complex was used under the standard conditions described in the literature[4c,21] (BF_3·AcOH, MeOH, 0 °C) once again no reaction occurred after 12 h, so we had to carry out the reaction at room temperature to give compound **17** in 60% yield after 12 h. All attempts to improve the yield by increasing the temperature were unsuccessful, because at 40 °C we observed deprotection of the *N*-Boc group. Taking into account that the cleavage of the acetonide moiety of **16** would not provide an acceptable yield, we decided to try using $Sc(OTf)_3$ (10 mol %) as a Lewis acid catalyst,[19] and we then obtained compound **17** in an almost quantitative yield after 24 h at 25 °C. The reaction temperature is critical to the success of the reaction, because at 40 °C we observed deprotection of the *N*-Boc group.

Alcohol **17** was converted into (*R*)-Iva (**6**) as follows. It was oxidized by treatment with Jones reagent to give the corresponding protected amino acid, which was then subjected to hydrolysis using a mixture of concentrated HCl and THF at room temperature. Liberation of the amino acid from its hydrochloride salt was then achieved by treating with propylene oxide in ethanol at reflux to furnish (*R*)-Iva (**6**) in high yield. The spectral data and optical activity of this compound proved to be identical to that previously reported.[10]

The enantiomer of (*R*)-Iva, (*S*)-Iva (**7**), was obtained using the same strategy but starting from (*R*)-α-methylserinal **4**, which was transformed into olefin **18**, as shown in Scheme 4. Hydrogenation of **18** gave oxazolidine **19,** and the subsequent cleavage of its acetonide moiety allowed the synthesis of alcohol **20**, the direct precursor of the desired amino acid **7**, whose spectral data were identical to that previously obtained for amino acid **6** but with an optical rotation of opposite sign.

Determination of Enantiomeric Purity. The optical purity of starting material **5**, purchased from Lancaster, was determined by preparation of its Mosher esters (Scheme 5). According to the protocol described in the literature,[2a,22] glycidol **5** was coupled with (*R*)-(+)-methoxytrifluorophenylacetic acid [(*R*)-(+)-MTPA] in the presence of DCC and DMAP to give the Mosher ester **21**. Analysis of the ^1H NMR spectra of ester **21** showed that the enantiomeric purity of compound **5** was 94%. In any case, to be sure that compound **5** was almost enantiomerically pure, we determined the cross-contamination by conversion of this compound to its Mosher ester derivative **22**, coupling **5** in the same conditions with (*S*)-(−)-methoxytrifluorophenylacetic acid [(*S*)-(−)-MTPA].

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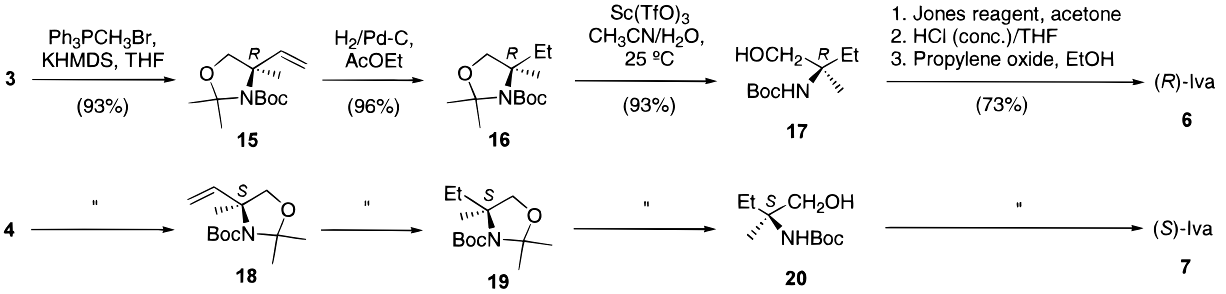
[19] $Sc(OTf)_3$ was discovered by Kobayashi et al. to be a new type of water-soluble Lewis acid (Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755−3758), and convenient procedures for deprotection of silyl ethers using a catalytic amount of $Sc(OTf)_3$ have been developed (Kobayashi, S.; Oriyama, T,; Noda, K. *Synlett.* **1998**, 1047−1048).

[20] Beaulieu, P. L.; Duceppe, J.-S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196−4204.

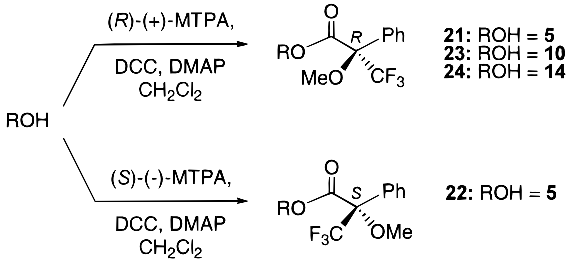
[21] Williams, L.; East, S. P.; Shao, F.; Joullié, M. M. *Tetrahedron* **1998**, *54*, 13371−13390.

[22] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

Scheme 4



Scheme 5



The enantiomeric purity of the intermediates in the synthesis of building blocks **3** and **4** was examined by derivatization of alcohol intermediates **10** and **14**. Because **10** and **14** are enantiomers, we only needed to use (*R*)-(+)-MTPA to obtain diastereomers **23** and **24**. In this case, the analysis of their ^{19}F NMR spectra showed that the enantiomeric purity was 94% for both compounds.

The enantiomeric purity of methylserinals **3** and **4** was checked by means of ^{1}H NMR, using an europium(III) chelate as a chiral shift reagent (94% and >95% ee, respectively). Different chemical shifts for the aldehyde proton were observed when a 0.09 molar ratio of Eu(hfc)$_3$/substrate and a concentration of substrate of 0.2 mmol/ml in deuterated chloroform at 20 °C were used.[23] Thus, no racemization could be detected by ^{1}H NMR.

The optical rotation found for methylserinal **3** was near to that previously described,[9] and the optical rotation of methylserinal **4** was identical to that found for **3** but opposite in sign. Because the optical rotation value of methylserinal **4** had not been previously reported, the absolute configuration of this compound was confirmed by converting serinal **3** and **4** to known Iva **6** and **7**, respectively. The absolute configurations of building blocks **3** and **4** were thus confirmed as the (*S*)- and (*R*)-forms, respectively.

The $[\alpha]^{25}_D$ values of Iva **6**, $[\alpha]^{25}_D = -10.8$ (c 1.00, H_2O), and Iva **7**, $[\alpha]^{25}_D = +10.9$ (c 1.00, H_2O), confirmed their chiral purity as well as the absolute configuration assigned to all compounds.

We were unable to use HPLC on the chiral phase[24] to determine the enantiomeric ratio of **6** and **7**, as no separation of both enantiomers could be achieved.

Conclusion

We report a large scale and stereodivergent synthesis of both enantiomers of (*S*)- and (*R*)-Garner's aldehyde homologues, the α-methyl derivatives **3** and **4**, starting from commercially available (*R*)-2-methylglycidol (**5**). These compounds have proved to be valuable starting materials in a new approach to the synthesis of both (*S*)- and (*R*)-Iva.

Other applications of α-methylserinals **3** and **4** are currently under investigation to explore the scope of their behavior as building blocks in asymmetric synthesis of α-methylamino acids.

Experimental Section

General Procedures. Melting points are uncorrected. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. Lewis acids and other chemical reagents were purchased from the Aldrich Chemical Co. or Acros Organics. Analytical TLC was performed by using Polychrom SI F$_{254}$ plates. Column chromatography was performed by using Kieselgel 60 (230−400 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, were concentrated under reduced pressure using a rotary evaporator. Optical rotations were measured in 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively. Values for υ_{max} (cm^{-1}) of IR spectra are given for the main absorption bands. Compound **8** was prepared according to procedures in the literature.[15] NMR spectra were recorded at 300 (^{1}H) and at 75 (^{13}C) MHz and are reported in ppm downfield from TMS. Mass spectra were obtained by electron impact (EI) or electrospray ionization (ESI) techniques. Nitrogen inversion in the oxazolidine ring or slow interconversion of both amide or carbamate conformers of compounds **3**, **4**, **9**, **10**, **13**−**16**, **18**, **19**, **23**, and **24** causes considerable line broadening and duplication of signals in the ^{1}H and ^{13}C NMR spectra.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(pivaloyloxy)methyl-2,2,4-trimethyl-3-oxazolidine (9). Alcohol **8** (3.61 g, 12.5 mmoL) was dissolved in a mixture of acetone (50 mL) and DMP (15 mL), and then $BF_3{\cdot}OEt_2$ (0.1 mL) was added. The resulting solution was stirred at room temperature for 2 h. The solvent was removed, and the residual oil was taken up in CH_2Cl_2 (50 mL). The resulting solution was washed with a mixture of saturated $NaHCO_3$ and H_2O (1:1 v/v, 30 mL) and then brine (30 mL) and dried, and the solvent was evaporated to give a yellow oil, which was purified by column chromatography (hexane/ethyl acetate, 9:1) to give **9** (3.71 g, 90%) as a white solid. Mp 44−45 °C. $[\alpha]^{25}_D = -14.9$ (c 1.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.20, 1.21 (2s, 9H), 1.36, 1.44 (2s, 3H), 1.47 (s, 9H), 1.54, 1.58, 1.59 (3s, 6H), 3.66 ("t", 1H, $J = 8.7$ Hz), 3.93, 3.99 (2d, 1H, $J = 8.7, 9.0$ Hz), 4.14, 4.18 (2d, 1H, $J = 8.1, 10.8$ Hz), 4.22, 4.30 (2d, 1H, $J = 8.4, 10.5$ Hz). ^{13}C NMR ($CDCl_3$) δ 20.2, 21.3, 25.0, 25.5, 26.2, 26.6, 27.1, 28.4, 38.8, 60.8, 61.7, 65.0, 65.5, 71.6, 72.0, 80.0, 80.2, 94.8, 95.8, 151.2, 151.4, 177.9, 178.0. IR (CH_2Cl_2) 1725, 1691, 1390, 1376, 1368. MS(EI) (m/z) = 41, 57, 114, 158, 214, 314. ESI+ (m/z) = 330. Anal. Calcd for

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[23] (**3** + **4**) without Eu(hfc)$_3$ δ (HC=O): two singlets centered at 9.39 and 9.46 ppm, respectively, corresponding to duplication of signals. (**3** + **4**) with Eu(hfc)$_3$ δ (HC=O): two singlets centered at 9.78 and 9.95 ppm of (*S*)-isomer and two singlets at 9.79 and 9.89 ppm corresponding to the splitting in the other isomer by the action of Eu(hfc)$_3$.

[24] The HPLC analysis used columns with the chiral phases Crownpak-CR(+) and Chiralcel-OD-H, purchased from Daicel Chemical.

$C_{17}H_{31}NO_5$: C, 61.98; H, 9.48; N, 4.25. Found: C, 62.57; H, 9.60; N, 4.16.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-4-hydroxymethyl-2,2,4-trimethyl-3-oxazolidine (10). Compound **9** (3.57 g, 10.8 mmol) was dissolved in CH_2Cl_2 (50 mL), and the solution was cooled to −78 °C before addition of DIBAL-H (1.0 M in CH_2Cl_2, 22.7 mL, 22.7 mmol). Stirring was continued for 12 h before addition of MeOH (5 mL) and warming to room temperature. The mixture was then poured into a solution of potassium sodium tartrate (25.0 g) in H_2O (75 mL), and the biphasic mixture was stirred vigorously for 2 h. The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried and evaporated to give **10** (2.52 g, 95%) as a white solid, which was used without further purification. Mp 59−60 °C. $[\alpha]^{25}_D = +1.3$ (*c* 1.99, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.43, 1.49, 1.56 (3s, 18H), 3.52−3.75 (m, 4H), 4.55, 4.57 (2brs, 1H). ^{13}C NMR ($CDCl_3$) δ 19.5, 20.8, 25.2, 25.6, 27.1, 28.4, 64.6, 65.6, 67.7, 72.1, 80.9, 95.3, 153.4. IR (CH_2Cl_2) 3381, 1687, 1663, 1397, 1378, 1368. MS(EI) (*m/z*) = 41, 57, 114, 130, 158, 214, 246. ESI+ (*m/z*) = 246. Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.74, H, 9.53; N, 5.68.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-4-formyl-2,2,4-trimethyl-3-oxazolidine (3). DMSO (2.23 g, 28.6 mmol) was added, at −78 °C, to a solution of oxalyl chloride (2.18 g, 17.2 mmol) in CH_2Cl_2 (30 mL). The resulting solution was stirred for 5 min at −78 °C, and then a solution of **10** (3.52 g, 14.3 mmol) in CH_2Cl_2 (30 mL) was added. The resulting mixture was stirred for 15 min at −78 °C, and then Et_3N (5.79 g, 57.2 mmol) was added. The solution was allowed to warm to room temperature. The reaction was quenched by addition of saturated $NaHCO_3$ (70 mL) and then diluted with Et_2O (70 mL). The phases were separated, and the organic phase was washed with 1 M $KHSO_4$ (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL), dried, filtered, and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate, 9:1) to give **3** (3.34 g, 96%) as a white solid. Mp 54−55 °C. $[\alpha]^{25}_D = -20.0$ (*c* 2.13, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.30−1.70 (m, 18H), 3.65, 3.68 (2d, 1H, J = 6.9 Hz), 3.92 (d, 1H, J = 9.3 Hz), 9.39, 9.46 (2s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.2, 18.1, 24.5, 25.5, 26.0, 26.9, 28.0, 28.2, 68.5, 68.9, 69.0, 69.2, 81.2, 81.3, 94.9, 96.0, 150.5, 151.7, 197.9, 198.4. IR (CH_2Cl_2) 1699, 1368, 1354. MS(EI) (*m/z*) = 41, 57, 114, 214. ESI+ (*m/z*) = 244. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.52; H, 8.76; N, 5.71.

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methyl-1-(pivaloyloxy)propane (11). Alcohol **8** (2.05 g, 7.1 mmol) was dissolved in DMF (30 mL),and TBDPSCl (3.90 g, 14.2 mmol) was added. The mixture was cooled to 0 °C, and imidazole (0.97 g, 14.2 mmol) was added portionwise over 5 min. The cooling bath was removed, and the mixture was stirred for 48 h at 25 °C. The solvent was removed, and the residual oil was taken up in ethyl acetate. The resulting solution was washed with H_2O (50 mL), dried, filtered,and concentrated to give a colorless oil, which was purified by column chromatography (hexane/ethyl acetate, 9:1) to give **11** (3.18 g, 85%) as a colorless oil. $[\alpha]^{25}_D = -1.9$ (*c* 1.20, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.14 (s, 9H), 1.34 (s, 3H), 1.42 (s, 9H), 3.60, 3.68 (2d, 2H, J = 9.0 Hz), 4.22, 4.30 (2d, 2H, J = 9.0 Hz), 4.78 (brs, 1H), 7.30−7.45 (m, 6H), 7.55−7.70 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 19.2, 19.3, 26.8, 27.1, 28.4, 38.8, 55.8, 65.2, 66.2, 79.1, 127.8, 129.8, 132.9, 135.5, 154.6, 177.9. IR (CH_2Cl_2) 1724. MS(EI) (*m/z*) = 41, 57, 438. ESI+ (*m/z*) = 528. Anal. Calcd for $C_{30}H_{45}NO_5Si$: C, 68.27; H, 8.59; N, 2.65. Found: C, 68.15; H, 8.51; N, 2.71.

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanol (12). Starting from compound **11** (2.71 g, 5.2 mmol) and in a similar way to that described for compound **10**, alcohol **12** (1.64 g, 71%) was obtained as a white solid. Mp 62−63 °C. $[\alpha]^{25}_D = -0.2$ (*c* 0.98, MeOH). ^1H NMR ($CDCl_3$) δ 1.08 (s, 9H), 1.23 (s, 3H), 1.44 (s, 9H), 1.61 (brs, 1H), 3.53−3.77 (m, 4H), 5.12 (brs, 1H), 7.30−7.45 (m, 6H), 7.55−7.65 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 19.2, 19.8, 26.8, 28.3, 57.3, 67.5, 68.0, 79.5, 127.7, 129.8, 132.7, 132.8, 135.5, 156.0. IR (CH_2Cl_2) 3424, 1715, 1696. MS(EI) (*m/z*) = 41, 56, 100, 181, 191, 211, 234, 312. ESI+ (*m/z*) = 444. Anal. Calcd for $C_{25}H_{37}NO_4Si$: C, 67.68; H, 8.41; N, 3.16. Found: C, 67.49; H, 8.33; N, 3.23.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-4-((*tert*-butyldiphenylsilyloxy)methyl)-2,2,4-trimethyl-3-oxazolidine (13). A solution of **12** (2.54 g, 5.70 mmol), DMP (1.19 g, 11.4 mmol), and TsOH (11 mg, 0.06 mmol) in toluene (60 mL) was heated under reflux for 2 h and then slowly distilled during 15 min to eliminate the MeOH formed. After that, DMP (1.19 g, 11.4 mmol) was added, and the procedure was repeated twice. After this time, the TLC showed no remaining starting material and clean formation of a single product. The solvent was removed to give a yellow oil, which was purified by column chromatography (hexane/ethyl acetate, 19:1) to give **13** (2.59 g, 94%) as a white solid. Mp 71−73 °C. $[\alpha]^{25}_D = +5.2$ (*c* 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.05, 1.06 (2s, 9H), 1.28, 1.51, 1.52 (3s, 9H), 1.37 (s, 3H), 1.48, 1.56 (2s, 6H), 3.55−3.75 (m, 2.6H), 4.05 (d, 0.4H, J = 9.6 Hz), 4.20, 4.26 (2d, 1H, J = 8.7 Hz), 7.30−7.45 (m, 6H), 7.58−7.73 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 19.3, 20.1, 21.0, 25.1, 25.5, 26.0, 26.8, 27.1, 28.3, 28.5, 62.9, 63.9, 64.4, 66.1, 71.6, 72.2, 79.6, 94.8, 95.6, 127.6, 127.7, 129.6, 129.7, 133.2, 133.4, 135.6, 151.3, 151.7. IR (CH_2Cl_2) 1688, 1392, 1376, 1367. MS(EI) (*m/z*)= 42, 57, 97, 114, 368. ESI+ (*m/z*)= 484. Anal. Calcd for $C_{28}H_{41}NO_4Si$: C, 69.52; H, 8.54; N, 2.90. Found: C, 69.62; H, 8.65; N, 2.87.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-4-hydroxymethyl-2,2,4-trimethyl-3-oxazolidine (14). A solution of $Bu_4N^+F^- \cdot 3H_2O$ (2.73 g, 8.68 mmol) in THF (20 mL) was added to a solution of compound **13** (2.80 g, 5.83 mmol) in THF (30 mL) at room temperature. The mixture was stirred for 24 h at room temperature. After this time, the TLC showed no remaining starting material. The solvent was removed to give a brown solid, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **14** (1.23 g, 88%) as a white solid. $[\alpha]^{25}_D = -1.6$ (*c* 1.99, $CHCl_3$). Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.68; H, 9.46; N, 5.71.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-4-formyl-2,2,4-trimethyl-3-oxazolidine (4). In a manner similar to that described for its enantiomer **3**, compound **4** (3.31 g, 96%) was obtained from alcohol **14** (3.51 g, 14.3 mmol). $[\alpha]^{25}_D = +19.2$ (*c* 2.12, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.58; H, 8.68; N, 5.88.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2,2,4-trimethyl-4-vinyl-3-oxazolidine (15). Methyltriphenylphosphonium bromide (4.98 g, 13.9 mmol) was suspended in THF (60 mL) at room temperature, and KHMDS (0.5*M* in toluene, 27.9 mL, 13.9 mmol) was added. The resulting yellow suspension was stirred at room temperature for 1 h and then cooled to −78 °C, and a solution of aldehyde **3** (1.13 g, 4.6 mmol) in THF (20 mL) was added dropwise. The cooling bath was removed, and the mixture allowed to reach room temperature over 2 h and then warmed to 35 °C for a further 12 h. The reaction was quenched with MeOH (10 mL), and the resulting mixture was poured into a solution of saturated potassium sodium tartrate and H_2O (1:1, v/v, 150 mL). Extraction with ethyl ether (2 × 75 mL), drying and evaporation of the solvent gave a pale yellow syrup, which was purified by flash chromatography (hexane/ethyl acetate, 4:1) to give **15** (1.03 g, 93%) as a colorless liquid. $[\alpha]^{25}_D = +5.0$ (*c* 2.16, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.30−1.64 (m, 18H), 3.70 (d, 1H, J = 8.7 Hz), 3.80 (d, 1H, J = 8.7 Hz), 5.00−5.20 (m, 2H), 5.80−6.04 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 21.8, 24.9, 25.6, 26.1, 26.8, 28.3, 62.9, 63.5, 74.6, 75.0, 79.6, 79.8, 94.6, 95.4, 113.0, 113.4, 141.0, 141.8, 151.0, 151.8. IR (CH_2Cl_2) 1687, 1385, 1366. MS(EI) (*m/z*) = 41, 57, 126, 170, 242. ESI+ (*m/z*)= 242. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.57; H, 9.58; N, 5.79.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-4-ethyl-2,2,4-trimethyl-3-oxazolidine (16). Palladium on carbon (1:10 catalyst/substrate by weight) was added to a solution of **15** (1.20 g, 5.0 mmol) in ethyl acetate (20 mL). The suspension was stirred at room temperature for 12 h. The catalyst was removed by filtration, and the solvent was evaporated to give **16** (1.17 g, 96%) as a colorless liquid, which was used without further purification. $[\alpha]^{25}_D = -1.7$ (*c* 1.83, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.80−0.90 (m, 3H), 1.33, 1.39 (2s, 3H), 1.48 (s, 9H), 1.50, 1.53, 1.54, 1.57 (4s, 6H), 1.58−1.78 (m, 1H), 1.79−2.00 (m, 1H), 3.58, 3.61 (2d, 1H, $J = 5.4$ Hz), 3.82, 3.85 (2d, 1H, $J = 3.6$ Hz). ^{13}C NMR ($CDCl_3$) δ 8.8, 8.9, 22.9, 24.4, 24.9, 25.4, 26.0, 26.7, 28.4, 28.6, 29.7, 62.3, 63.2, 72.7, 73.0, 79.2, 79.3, 94.3, 95.3, 151.2, 151.8. IR (CH_2Cl_2) 1686, 1391, 1374, 1366. MS(EI) (m/z) = 41, 57, 172, 228. ESI+ (m/z) = 244. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.02; H, 10.21; N, 5.60.

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-methylbutanol (17). Compound **16** (200 mg, 0.82 mmol) dissolved in acetonitrile (15 mL) and water (74 μL, 0.4 mmol) were added to a solution of $Sc(OTf)_3$ (40 mg, 0.08 mmol) in acetonitrile (5 mL), at 25 °C. This mixture was stirred for 24 h at 25 °C and quenched with a phosphate buffer (pH 7). The organic materials were extracted with ethyl acetate (3 × 20 mL), and the combined extracts were washed with brine and dried. The solvent was removed to obtain a yellow oil, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **17** (155 mg, 93%) as a white solid. Mp 57 °C. $[\alpha]^{25}_{D} = +4.1$ (c 1.00, MeOH). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, $J = 7.5$ Hz), 1.43 (s, 9H), 1.52 (s, 3H), 1.50−1.67 (m, 1H), 1.69−1.82 (m, 1H), 3.58, 3.64 (2d, 2H, $J = 11.4$ Hz), 4.39 (brs, 1H), 4.70 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 7.8, 21.9, 28.3, 29.0, 57.0, 69.4, 79.7, 156.2. IR (CH_2Cl_2) 3433, 1714, 1691. MS(EI) (m/z) = 41, 57, 72, 116, 174. ESI+ (m/z) = 204. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.94; H, 10.41; N, 6.79.

(*R*)-2-Amino-2-methylbutanoic Acid (6). A 1.5-fold excess of Jones reagent was dropwise added to a solution of **17** (200 mg, 0.98 mmol) in acetone (10 mL) at 0 °C over 5 min. The mixture was stirred at 0 °C for 3 h and then at room temperature for a further 3 h. The excess of Jones reagent was destroyed with 2-propanol. The mixture was then diluted with water (10 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were dried and concentrated. The residual yellow oil (187 mg) was dissolved in THF (15 mL) and treated with concentrated HCl (1 mL). The mixture was stirred at room temperature for 6 h. The solvent was removed, and the residual oil was partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was concentrated to give 2-amino-2-methylbutanoic acid hydrochloride as a white solid (129 mg). This compound was dissolved in EtOH/propylene oxide (3:1, 8 mL), and the mixture was heated under reflux for 2 h. After this time, the amino acid partially precipitated as a white solid (33 mg). The filtrate was concentrated, and the residue was dissolved in distilled water and eluted through a C_{18} reverse-phase Sep-pak cartridge to give, after removal of the water, 51 mg of **6** as a white solid; total amount 84 mg (73%). Mp > 300 °C. $[\alpha]^{25}_{D} = -10.8$ (c 1.00, H_2O). ^{1}H NMR (D_2O) δ 0.87 (t, 3H, $J = 7.5$ Hz), 1.42 (s, 3H), 1.65−1.78 (m, 1H), 1.80−1.92 (m, 1H). ^{13}C NMR (D_2O) δ 7.6, 22.2, 30.4, 62.1, 177.1. IR (Nujol, cm^{-1}) 3000−2250, 1600. ESI+ (m/z) = 118. Anal. Calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 50.03; H, 9.39; N, 11.87.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-2,2,4-trimethyl-4-vinyl-3-oxazolidine (18). In a manner similar to that described for its enantiomer **15**, compound **18** (1.02 g, 93%) was obtained from aldehyde **4** (1.12 g, 4.6 mmol). $[\alpha]^{25}_{D} = -5.1$ (c 2.16, $CHCl_3$). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.60; H, 9.54; N, 5.71.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-4-ethyl-2,2,4-trimethyl-3-oxazolidine (19). In a manner similar to that described for its enantiomer **16**, compound **19** (1.18 g, 96%) was obtained from compound **18** (1.20 g, 5.0 mmol). $[\alpha]^{25}_{D} = +1.4$ (c 1.82, $CHCl_3$). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.00; H, 10.30; N, 5.73.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-methylbutanol (20). In a manner similar to that described for its enantiomer **17**, compound **20** (153 mg, 93%) was obtained from compound **19** (201 mg, 0.82 mmol). $[\alpha]^{25}_{D} = -4.0$ (c 1.02, MeOH). Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 59.10; H, 10.39; N, 6.84.

(*S*)-2-Amino-2-methylbutanoic Acid (7). In a manner similar to that described for its enantiomer **6**, amino acid **7** (83 mg, 72%) was obtained from compound **20** (153 mg, 0.75 mmol). $[\alpha]^{25}_{D} = +10.9$ (c 1.00, H_2O). Anal. Calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 50.10; H, 9.34; N, 11.86.

Preparation of MTPA Esters. A solution of MTPA (71.8 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) was added to a solution of the alcohol (0.27 mmol), DCC (60.5 mg, 0.29 mmol), and DMAP (3.2 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred at room temperature for 4.5 h. The resulting white suspension was filtered to remove the *N*,*N′*-dicyclohexylurea. The filtrate was concentrated to give a white slurry, to which Et_2O was added. The resulting suspension was filtered to remove the *N*-acyl-*N′*-cyclohexylurea and then concentrated to give the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate, 9:1).

(2*S*,2′*R*)-2-((2′-Methoxy-2′-(trifluoromethyl)phenylacetyloxy)methyl)-2-methyloxirane (21). $[\alpha]^{25}_{D} = +46.6$ (c 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 2.64 (d, 1H, $J = 4.5$ Hz), 2.76 (d, 1H, $J = 4.8$ Hz), 3.55 (s, 3H), 4.22 (d, 1H, $J = 12.0$ Hz), 4.47 (d, 1H, $J = 12.0$ Hz), 7.35−7.45 (m, 3H), 7.50−7.60 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 18.2, 51.5, 54.3, 55.4, 68.1, 121.2, 125.1, 127.3, 128.4, 129.7, 131.9, 166.2. ^{19}F NMR ($CDCl_3$) δ −71.9. IR (CH_2Cl_2, cm^{-1}) 1753. MS(EI) (m/z) = 43, 77, 105, 189, 304. ESI+ (m/z) = 305. Anal. Calcd for $C_{14}H_{15}F_3O_4$: C, 55.26; H, 4.97. Found: C, 54.92; H, 5.08.

(2*S*,2′*S*)-2-((2′-Methoxy-2′-(trifluoromethyl)phenylacetyloxy)methyl)-2-methyloxirane (22). $[\alpha]^{25}_{D} = -29.2$ (c 0.33, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 2.66, 2.75 (2d, 2H, $J = 4.5$ Hz), 3.56 (s, 3H), 4.16, 4.50 (2d, 2H, $J = 12.0$ Hz), 7.36−7.45 (m, 3H), 7.48−7.60 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 18.2, 51.9, 54.4, 55.5, 68.8, 121.3, 125.1, 127.3, 128.4, 129.7, 131.9, 166.2. ^{19}F NMR ($CDCl_3$) δ −71.9. IR (CH_2Cl_2) 1753. MS(EI) (m/z) = 43, 77, 105, 189, 289. ESI+ (m/z) = 305. Anal. Calcd for $C_{14}H_{15}F_3O_4$: C, 55.26; H, 4.97. Found: C, 55.32; H, 5.01.

(4*S*,2′*R*)-*N*-(*tert*-Butoxycarbonyl)-4-((2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy)methyl)-2,2,4-trimethyl-3-oxazolidine (23). Mp 54−55 °C. $[\alpha]^{25}_{D} = +22.2$ (c 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.28−1.60 (m, 18H), 3.53, 3.54 (2s, 3H), 3.56−3.61 (m, 1H), 3.79, 3.86 (2d, 1H, $J = 9.0$ Hz), 4.38, 4.43 (2d, 1H, $J = 11.1$ Hz), 4.49, 4.55 (2d, 1H, $J = 10.8$ Hz), 7.35−7.45 (m, 3H), 7.46−7.55 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.9, 25.0, 25.3, 25.7, 26.7, 28.4, 55.4, 60.5, 61.3, 66.4, 67.0, 71.3, 71.7, 80.3, 80.6, 95.0, 96.0, 121.3, 125.2, 127.2, 128.4, 128.5, 129.6, 129.8, 131.8, 132.3, 151.3, 166.1, 166.2. ^{19}F NMR ($CDCl_3$) δ −71.9, −71.6. IR (CH_2Cl_2) 1751, 1692, 1391, 1376, 1368. MS(EI) (m/z) = 41, 57, 346. ESI+ (m/z) = 462. Anal. Calcd for $C_{22}H_{30}F_3NO_6$: C, 57.26; H, 6.55; N, 3.04. Found: C, 57.02; H, 6.49; N, 2.98.

(4*R*,2′*R*)-*N*-(*tert*-Butoxycarbonyl)-4-((2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy)methyl)-2,2,4-trimethyl-3-oxazolidine (24). Mp 49 °C. $[\alpha]^{25}_{D} = +31.7$ (c 1.28, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.35−1.55 (m, 18H), 3.52 (s, 3H), 3.57−3.63 (m, 1H), 3.81, 3.88 (m, 1H), 4.38, 4.51 (2brs, 2H), 7.35−7.45 (m, 3H), 7.46−7.55 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 19.9, 21.1, 25.1, 26.2, 26.3, 28.3, 28.4, 55.4, 60.4, 61.2, 67.0, 67.4, 71.5, 71.8, 80.4, 80.5, 95.0, 96.0, 121.3, 125.1, 127.3, 128.5, 129.7, 132.0, 151.4, 166.2. ^{19}F NMR ($CDCl_3$) δ −71.7, −71.6. IR (CH_2Cl_2) 1751, 1693, 1389, 1376, 1368. MS(EI) (m/z) = 41, 57, 346. ESI+ (m/z) = 462. Anal. Calcd for $C_{22}H_{30}F_3NO_6$: C, 57.26; H, 6.55; N, 3.04. Found: C, 57.20; H, 6.50; N, 3.09.

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Supporting Information Available: A full listing of ^{1}H and ^{13}C NMR data of all new compounds, complete with peak assignments. Copies of ^{1}H and ^{13}C NMR spectra, as well as ^{1}H−^{1}H and ^{1}H−^{13}C correlations for all new compounds. Zoom of the NMR signals in which the enantiomeric purity of **3**, **4**, **5**, **10**, and **14** was determined. This material is available free of charge via the Internet at http://pubs.acs.org.

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