Stereoselective Three-Carbon and Two-Carbon Elongation of the Carbon Chain in *N*-Boc-Protected α-Aminoacylsilanes: An Entry to Functionalized *β*-Amino Alcohols and to Statine Analogues

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The synthesis of enantiopure *β*-amino alcohols is currently a subject of enormous interest mainly due to their applications as peptidomimetics,[1] as building blocks for pharmaceuticals[2] and also as ligands for asymmetric catalysis.[3] Diastereoselective addition to α-amino aldehydes has emerged as one of the most efficient and versatile methods available for preparing functionalized *β*-amino alcohols.[4] However, *N*-protected α-amino aldehydes have some recurring drawbacks, since most of them are relatively unstable both chemically and configurationally, and low diastereoselectivity can be observed[5] in a number of addition reactions.

A simple conceptual approach to solve these problems, bypassing amino aldehydes, would be to consider amino acid-derived acylsilanes which mimic them and offer increased stability and higher diastereofacial selectivity induced by the presence of the bulky R_3Si moiety.[6]

We have previously reported[7] the synthesis of *N*-Pht-protected α- and *β*-aminoacylsilanes derived from L-phenylalanine and shown that the allylation occurs with good chemical yields and high diastereoselectivity. Extension of this previous work to differently protected α- and *β*-aminoacylsilanes obtained from L-phenylalanine indicated that stereoselectivity in the addition step is strongly dependent on the type of protecting group as well as on the nature of the allylating reagent.[8] Moreover, the robustness of the protecting groups so far employed (*N*-Pht and *N*-Ts) have caused some problems in the deprotection−desilylation steps of the allylated adducts, requiring harsh conditions.

These observations prompted us to extend our previous study to the synthesis of *N*-Boc aminoacylsilanes, since the Boc group has proven[9] highly serviceable in organic synthesis as an amine protecting group. Here we report the synthesis of the new *N*-Boc α-aminoacylsilanes derived from L-phenylalanine and L-isoleucine and their utility in a series of nucleophilic additions and aldol condensations with the aim of devising a new entry to functionalized molecules bearing the *β*-amino alcohol moiety.

The methodology previously used for the synthesis of aminoacylsilanes, based on the nucleophilic silylation of an acyl chloride,[7] was not applicable to the case of the N-Boc-protected amino acids due to formation of the corresponding oxazolone through spontaneous intramolecular cyclization.[10] On the other hand, attempts to use the Weinreb amides[11] from *N*-Boc-protected L-phenylalanine and L-isoleucine failed in the silylcupration reaction and led either to recovery of the starting materials or to intractable mixtures of products. The established usefulness and versatility of acylimidazolides,[12] also supported by our recent investigation directed at the synthesis of α-aminoketones,[13] prompted us to perform the silylcupration of these more activated forms of the amino acids. *N*-Boc L-phenylalanine (**1**) and *N*-Boc L-isoleucine (**2**) were converted (Scheme 1) into the corresponding α-aminoacylsilanes **5** and **6** in moderate yields via **3** and **4** by reaction with carbonyldiimidazole (CDI), followed by treatment with $(Me_2PhSi)_2CuCNLi_2$. These new compounds were purified by column chromatography on silica gel (see Experimental Section) and stored in a refrigerator for long periods without chemical degradation or racemization, thus proving their chemical and optical stability.[7,8]

The synthetic equivalence of **5** and **6** to α-amino aldehydes, which have been widely used in the synthesis of amino sugars[14] and other natural products,[1a,4a] allows

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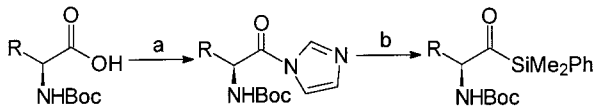
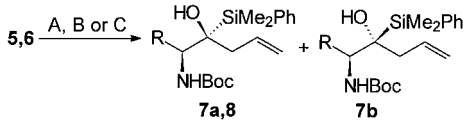
Scheme 1[a]



[a] (a) CDI, THF, rt, 45 min, 97% (for **3**), 98% (for **4**); (b) $(PhMe_2Si)_2CuCNLi_2$, −78 °C, 1 h, 50% (for **5**), 55% (for **6**).

Table 1. Asymmetric Allylation of 5 and 6



Entry	Substrate	R	Products	Conditions[a] A, B or C	Ratio syn:anti	Yield[b] (%)
1	**5**	$PhCH_2$	**7a** **7b**	A	20:80	61
2	**5**	$PhCH_2$	**7a** **7b**	B	35:65	96
3	**5**	$PhCH_2$	**7a** **7b**	C	65:35	61
4	**6**		**8**	A	99:1	60
5	**6**		**8**	B	99:1	95

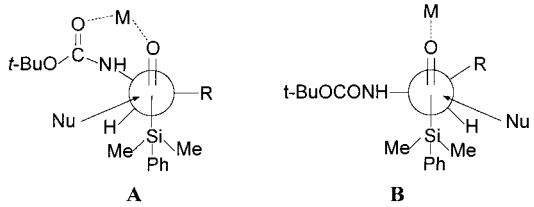
[a] Conditions A: 0.5 equiv of tetraallyltin, $Sc(OTf)_3$ (7 mol %), CH_2Cl_2, rt, 24 h; B: 2 equiv of allyl bromide, 1 equiv of In, THF, rt, 15 h; C: 3 equiv of allyltrimethylsilane, 2 equiv of $SnCl_4$, CH_2Cl_2, −78 °C, 12 h. [b] Yields of isolated products.

consideration of these new compounds as versatile chiral synthons with potential use in asymmetric synthesis. For this reason we embarked on a systematic three-carbon and two-carbon stereoselective elongation of the carbon skeleton of **5** and **6** via allylation and aldol reactions, respectively.

The results of the addition of the allyl moiety to the carbonyl group of **5** and **6** are shown in Table 1. Since the allylation under Hosomi−Sakurai conditions[15] led to extensive decomposition of the starting materials because of the incompatibility of $TiCl_4$ with the *N*-Boc moiety, we turned our attention to $Sc(OTf)_3$-catalyzed[16] allylation with tetraallyltin and In-mediated allylation with allyl bromide under Barbier conditions.[17] Both these reactions afforded the expected homoallylic alcohols in satisfactory to good yields.

Allylation of **5** under both conditions, A and B (entries 1 and 2), yielded a mixture of diastereoisomers, **7a** and **7b**, while similar additions to **6** afforded (entries 4 and 5) a single diastereoisomer **8** selectively. The choice of the allylating systems was made avoiding the use of more basic allylic metals to prevent racemization at the C_2 carbon in **5** and **6**.[18] To determine the configuration of the monoprotected diastereoisomeric adducts, **7a** and **7b**, separated by silica gel chromatography, and **8** were subjected to stereospecific protiodesilylation with TBAF, which can be assumed to proceed with complete retention of configuration,[6,19] to give the enantiopure β-amino alcohols **9a**,**b** and **12**.[18] Subsequent deprotection of the *N*-Boc group took place under normal conditions affording the isomerically pure amino alcohols **10a**,**b** and **13** in high yields. After their transformation into the corresponding oxazolidinone derivatives **11a**,**b** and **14**, their relative stereochemistry at C_2 and C_3 was determined by measuring the coupling constants ($J_{H4}-J_{H5}$) and observing the NOE cross-peak between the H-4 and H-5 protons[20] (Scheme 2). These results suggested that the absolute configuration of the carbon bearing the hydroxy group is *R* in products **7a** and **8**, and *S* in product **7b**.

The significant differences in diastereoselectivities in Table 1 appear related to the structure of the starting amino acid. The observation that under the same allylation conditions only derivative **6** leads to very high *syn* selectivity suggests that factors other than chelation are likely to play a major role in driving the stereochemical outcome. Based on the Felkin−Ahn model, we propose that these reactions proceed via conformers **A** and **B**.



The increase in the level of *syn* amino alcohol, which accompanies the α-branching of the side chain as in **6**, can be concisely rationalized in terms of increased adoption of conformer **A** in order to minimize steric interaction of R with the Lewis acid- or In-coordinated[21] carbonyl group. Chelation might also be operational in stabilizing this conformer. As the spatial demand of R is reduced as in the case of **5**, conformer **B** would be favored and *anti* selectivity materializes. In this case, however, the differences in the product ratios are modest, indicating a small energy difference between the two pathways. In the $SnCl_4$-promoted reaction of **5** the diastereoselectivity is biased in the *syn* direction as a consequence of a chelation[22] of the Lewis acid by both the oxygen atoms of the Boc and carbonyl moieties thus favoring **A**.

Stereoselective two-carbon elongation of the carbon skeleton of aminoacylsilanes **5** and **6** was performed by introducing an acetic acid moiety. The aldol reaction of *O*-ethyl-*O*-*tert*-butyldimethylsilyl ketene acetal with **5** and **6** proceeded smoothly (Scheme 3) in the presence of $BF_3{\cdot}Et_2O$ to give the expected addition products **15a**,**b** and **17** in good yields and with high diastereoselectivity in favor of the *syn* adduct. The highly preferred *syn* selectivities can be accounted for by a preferential attack

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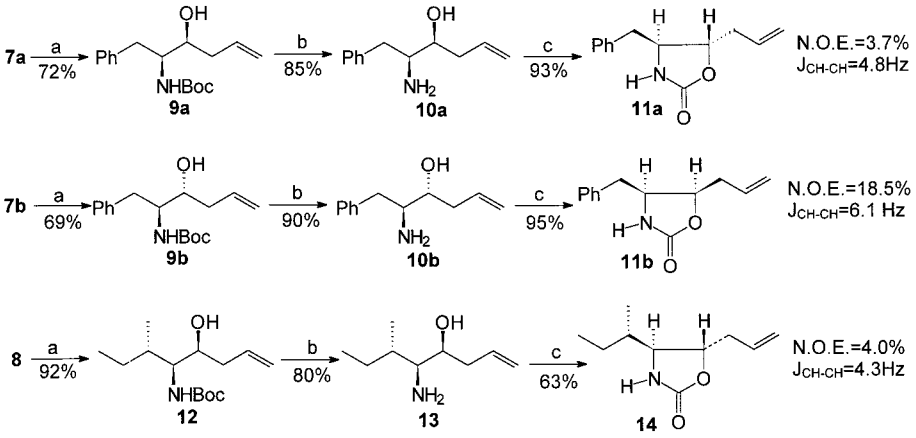
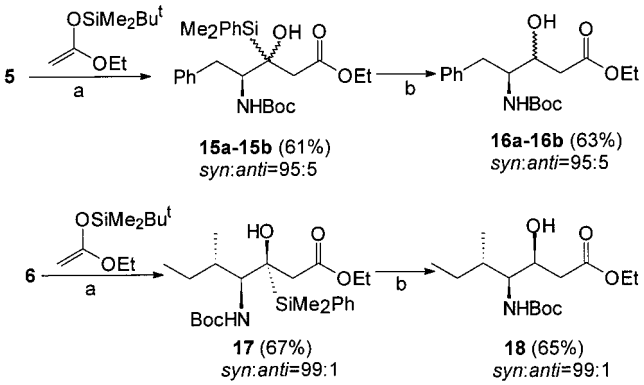
Scheme 2[a]



[a] (a) TBAF, THF, rt, 24 h; (b) 4 N HCl/dioxane, 1 h, rt, (c) CDI, DMAP (12% mol), THF, rt, 24 h.

Scheme 3[a]



[a] Conditions: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 48 h for **5**, 10 h for **6**; (b) TBAF, THF, rt, 24 h.

on the less hindered *Si* face[23] of the starting acylsilanes in which the $BF_3{\cdot}Et_2O$ predominantly coordinates the carbonyl oxygen.

The stereochemistry of **15a**,**b** and **17** was determined after desilylation of the compounds with TBAF by comparison of the spectroscopic data of **16a**,**b** and **18** with the literature data.[24] The *syn*:*anti* ratios in Scheme 3 appear slightly higher with respect to those obtained with the same Lewis acid in the diastereoselective addition of silyl ketene acetals to *N*-protected α-amino aldehydes,[25] providing further support to the assumption that a beneficial effect can be exerted by the R_3Si moiety on the diastereofacial selectivity. A set of important biologically active statine analogues with natural configurations (3*S*,4*S*) can be prepared by this four-step highly *syn*-diastereoselective sequence. The difficulties due to low diastereoselectivities with the presence of the incorrect 3*R*,4*S* and the severe reaction conditions[26] can be overcome with this procedure, which nicely complements the more recent reports[27] on the preparation of this class of compounds.

The methodology outlined herein based on the three-carbon and two-carbon elongation of the carbon chain of several new *N*-Boc-protected α-aminoacylsilanes via nucleophilic addition to the carbonyl moiety constitutes a convenient and reliable means for the stereoselective synthesis of functionalized amino alcohol units frequently found as key structural units in bioactive compounds. Extension to other two-carbon elongation procedures calls for further studies now in progress in our laboratory.

Experimental Section

General. Capillary mp are uncorrected. NMR spectra were recorded as follows: ^{1}H NMR (200 and 300 MHz; $CDCl_3$, δ = 7.23 ppm) and ^{13}C NMR (50.3 and 75.46 MHz, δ = 77.0 ppm). Mass spectra were recorded at an ionizing voltage of 70 eV. Infrared spectra were taken in CCl_4. Optical rotations were determined as solutions in a 1-dm cell. Combustion analyses were performed by the analysis service of the University of Florence. Moisture sensitive reactions were carried out in oven-dried (120 °C) glassware under an Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with the standard syringe/septum technique. THF was distilled immediately prior to use from benzophenone ketyl under Ar. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 just prior to use. Other solvents were purified by standard procedures. Petroleum ether refers to the fraction bp 40−60 °C. The reactions were monitored by TLC on silica gel plates. Column chromatography was performed with 70−230 mesh silica gel 60. Preparative TLC was carried out on glass plates using a 1 mm layer. The ratios between the diastereoisomers of the diastereomeric mixtures were determined from the ^{1}H NMR spectra of the crude products by integration of well-separated signals. In the case of compounds whose NMR spectra indicate the presence of a single diastereoisomer (**8**, **12**−**14**, **17**, **18**) the estimate of the de values derives from a measure of the signal-to-noise ratio of the ^{1}H NMR spectra of the crude products.

Preparation of Imidazolides: Typical Procedure. To a solution of *N*-(*tert*-butoxycarbonyl)-L-phenylalanine **1** (1.59 g, 6.0 mmol) in THF (6.0 mL) was added 1.07 g (6.6 mmol) of *N*,*N*′-carbonyldiimidazole at room temperature. The reaction mixture was stirred at the same temperature for 30 min, diluted with Et_2O, and quenched with water. The organic layer was washed twice with distilled water, dried over $MgSO_4$, filtered, and concentrated in vacuo giving 1.84 g (97%) of **(2*S*)-2-[*N*-(*tert*-**

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Butoxycarbonyl)amino]-1-imidazol-1-yl-3-phenylpropan-1-one (3). White solid, mp 110 °C; $[\alpha]^{24}_D$ +33.1° (*c* 2.00, $CHCl_3$); IR: 3440, 1740, 1720 cm^{-1}; MS (EI) *m/z* 248 (M^+- $C_3H_3N_2$), 192, 164, 120; ^1H NMR (200 MHz) δ 1.40 (s, 9H), 3.06 (dd, 1H, J = 13.9, 6.2 Hz), 5.15 (m, 1H), 5.33 (d, 1H, J = 7.5 Hz), 7.06 (s, 1H), 7.10−7.35 (m, 5H), 7.45 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (50.3 MHz) δ 28.1, 38.9, 54.7, 80.3, 116.0, 127.5, 128.8, 129.1, 131.2, 134.7, 136.4, 169.1.

(2*S*,3*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-1-imidazol-1-yl-3-methylpentan-1-one (4). Colorless oil (1.65 g, 98%), $[\alpha]^{24}_D$ +34.8° (*c* 3.59, $CHCl_3$); IR 3460, 1745, 1725 cm^{-1}; MS (EI) *m/z* 214 (M^+ − $C_3H_3N_2$), 158, 130; ^1H NMR (200 MHz) δ 0.85−1.05 (m, 6H), 1.10−2.00 (m, 12H), 4.82 (m, 1H), 5.38−5.42 (m, 1H), 7.13 (s, 1H), 7.55 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (50.3 MHz) δ 11.5, 16.2, 24.6, 28.6, 38.1, 58.5, 80.9, 116.8, 131.5, 137.0, 156.1, 170.4.

Synthesis of α-Aminoacylsilanes: Typical Procedure. Phenyl dimethylsilyllithium[28] (0.85 M, 35.5 mL, 30.17 mmol) was added to a suspension of CuCN (1.25 g, 15.07 mmol) in THF (70 mL) at 0 °C. The reaction mixture was stirred for 20 min under Ar atmosphere and then was slowly transferred by cannula to a suspension of **3** (4.31 g, 13.7 mmol) in THF (90 mL) at −78 °C. Stirring was continued at this temperature for further 30 min. Saturated aqueous NH_4Cl was then added to the solution, and the mixture was allowed to warm to room temperature and extracted three times with Et_2O (3 × 30 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography on silica gel (petroleum ether: Et_2O = 4:1), affording 2.62 g (50%) of **(2*S*)-3-Phenyl-2-[*N*-(*tert*-butoxycarbonyl)amino]propanoyldimethylphenylsilane (5)** as a light yellow oil. $[\alpha]^{24}_D$ +19.3 (*c* 2.00, $CHCl_3$); IR: 3420, 1715, 1650, 1240 cm^{-1}; MS (EI)-*m/z* 383 (M^+), 298, 221, 164, 135, 91, 57; ^1H NMR (200 MHz) δ 0.55 (s, 6H), 1.40 (s, 9H), 2.50 (dd, 1H, J = 14.0, 7.4 Hz), 2.95 (dd, 1H, J = 14.0, 5.8 Hz), 4.70 (bq, 1H, J = 7.6 Hz), 4.95 (d, 1H, J = 9.9 Hz), 6.80−6.95 (m, 2H), 7.20−7.80 (m, 8H); ^{13}C NMR (50.3 MHz) δ −4.6, −4.4, 28.2, 35.6, 64.2, 79.5, 126.5, 128.3, 128.3, 129.3, 130.1, 134.0, 134.1, 136.0, 154.8, 241.6. Anal. Calcd for $C_{22}H_{29}NO_3Si$: C, 68.90; H, 7.63; N, 3.65. Found: C, 68.82; H, 7.58; N, 3.61.

(2S,3S)-3-Methyl-2-[*N*-(*tert*-butoxycarbonyl)amino]pentanoyldimethylphenylsilane (6). The title compound was prepared by the procedure as described for compound **5**, using **4** (4.2 g, 15.0 mmol) and 16.5 mmol of phenyl dimethylsilyllithium cyanocuprate. Column chromatography on silica gel (petroleum ether: Et_2O = 6:1) gave 2.88 g (55%) of **6** as a pale yellow oil. $[\alpha]^{24}_D$ +62.6 (*c* 2.00, $CHCl_3$); IR: 3440, 1730, 1650, 1240 cm^{-1}; MS (EI) *m/z* 349 (M^+), 232, 220, 186, 135, 86, 57; ^1H NMR (300 MHz) δ 0.48−0.87 (m, 12H), 1.45−1.85 (m, 12H), 4.50 (dd, 1H, J = 8.9, 3.2 Hz), 5.05 (bd, 1H, J = 8.3 Hz), 7.30−7.60 (m, 5H); ^{13}C NMR (50.3 MHz) δ − 4.4, 11.3, 16.4, 23.0, 28.3, 34.8, 68.7, 79.3, 128.2, 130.0, 132.9, 133.9, 155.8, 243.0. Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.95; N, 4.01. Found: C, 65.27; H, 8.93; N, 4.00.

Sc(OTf)$_3$-Catalyzed Allylation of 5. To a stirred suspension of scandium(III) triflate (172.0 mg, 0.35 mmol) and tetraallyltin (0.61 mL, 716 mg, 2.53 mmol) in CH_2Cl_2 (20 mL) was added a solution of **5** (1.94 g, 5.07 mmol) in CH_2Cl_2 (40 mL) at room temperature. After 24 h, saturated aqueous NH_4Cl was added to the solution, and the mixture was extracted three times with Et_2O. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The ^1H NMR spectrum of the crude, showed the presence of both ***syn*-(2*S*,3*R*)-2-[*N*-(*tert*-butoxycarbonyl)-amino]-3-dimethylphenylsilyl-1-phenyl-5-hexen-3-ol (7a)** and ***anti*-(2*S*,3*S*)-2-[*N*-(*tert*-butoxycarbonyl)amino]-3-[dimethyl(phenyl)silyl]-1-phenyl-5-hexen-3-ol (7b)** isomers in a 20:80 ratio. The two isomers were separated by column chromatography on silica gel (CH_2Cl_2 as eluant) giving 1.03 g (48%) of **7b** as the less retained compound and 0.28 g (13%) of **7a** as the more retained compound, as pale yellow oils.

***syn*-7a:** $[\alpha]^{24}_D$ −11.1 (*c* 2.00, $CHCl_3$); IR: 3420, 1740 cm^{-1}; MS (EI) *m/z* 425 (M^+), 308, 135, 120, 91, 57; ^1H NMR (200 MHz) δ 0.45 (s, 6H), 1.00 (br s, 1H), 1.20 (s, 9H), 2.25−2.45 (m, 2H), 2.55 (dd, 1H, J = 14.3, 6.5 Hz), 2.90 (d, 1H, J = 12.3 Hz), 3.90 (td, 1H, J = 11.0, 2.3 Hz), 4.10 (d, 1H, J = 8.7 Hz), 5.00−5.20 (m, 2H), 5.85−6.10 (m, 1H), 6.90−7.05 (m, 2H), 7.10−7.15 (m, 3H), 7.30−7.45 (m, 3H), 7.60−7.70 (m, 2H); ^{13}C NMR (50.3 MHz) δ −3.2, −3.6, 28.1, 37.3, 41.4, 58.7, 72.5, 79.4, 118.5, 126.2, 128.0, 128.2, 128.9, 129.4, 133.4, 134.5, 137.5, 138.5, 156.77. Anal. Calcd for $C_{25}H_{35}NO_3Si$: C, 70.55; H, 8.30; N, 3.29. Found: C, 70.49; H, 8.26; N, 3.25.

***anti*-7b:** $[\alpha]^{24}_D$ −23.9 (*c* 2.00, $CHCl_3$); IR: 3430, 1730, 1250 cm^{-1}; MS (EI) *m/z* 425 (M^+), 308, 135, 120, 91, 57; ^1H NMR (200 MHz) δ 0.48 (s, 6H), 1.20 (br s, 1H), 1.41 (s, 9H), 2.35−2.40 (m, 2H), 2.60−2.70 (m, 1H), 2.95 (dd, 1H, J = 14.0, 2.7 Hz), 3.80−3.90 (m, 1H), 4.45 (d, 1H, J = 9.3 Hz), 5.20−5.40 (m, 2H), 5.80−6.20 (m, 1H), 7.00−7.10 (m, 2H), 7.15−7.25 (m, 3H), 7.30−7.40 (m, 3H), 7.60−7.72 (m, 2H); ^{13}C NMR (50.3 MHz) δ −3.6, −3.8, 28.2 34.8, 41.0, 57.9 72.0, 79.4 118.2, 126.1 127.8, 128.2 129.1 134.0, 134.6 137.4, 138.6, 156.1. Anal. Calcd for $C_{25}H_{35}NO_3Si$: C, 70.55; H, 8.30; N, 3.29. Found: C, 70.51; H, 8.26; N, 3.27.

Indium-Mediated Allylation of 5. Allyl bromide (2.05 mmol, 0.177 mL) was added to a mixture of **5** (335 mg, 0.87 mmol) and indium powder (110 mg, 0.96 mmol) in 3 mL of THF at room temperature. After stirring at the same temperature under nitrogen atmosphere for 15 h, the reaction mixture was poured into 5% aqueous Na_2CO_3. The organic layer was extracted with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel afforded 355 mg (96%) of the two diastereoisomers, *syn*-**7a** and *anti*-**7b**, in a 35:65 ratio. When the reaction was carried out in 3 mL of THF:H_2O 2:1 for 70 h, 270 mg (73%) of the two stereoisomers were obtained in the same ratio.

$SnCl_4$-Mediated Allylation of 5. A 100 mg (0.26 mmol) amount of **5** was mixed with 0.12 mL (0.78 mmol) of allyltrimethylsilane in 3 mL of CH_2Cl_2 at room temperature, and a 1 M solution of $SnCl_4$ in CH_2Cl_2 (0.52 mmol) was added to the solution at −78 °C. The reaction mixture was quenched after 12 h at −78 °C with saturated aqueous $NaHCO_3$ and extracted three times with Et_2O (3 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude was purified with preparative silica gel plates affording 67 mg of the two diastereostereoisomers, *syn*-**7a** and *anti*-**7b**, in a 65:35 ratio.

(2*S*,3*S*)-1-Phenyl-2-[*N*-(*tert*-butoxycarbonyl)amino]-5-hexen-3-ol (9a). To a stirred solution of α-hydroxysilane **7a** (500 mg, 1.18 mmol) in dry THF (15 mL) was added a 1.0 M solution of TBAF (1.30 mL, 1.30 mmol) in THF at room temperature. The reaction mixture was stirred under Ar atmosphere at the same temperature for 24 h, and saturated aqueous NH_4Cl and then Et_2O (50 mL) were added to the solution. The organic layer was washed three times with water and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the crude was submitted to ^1H NMR analysis which showed the presence of a single diastereoisomer. The crude was then purified by column chromatography on silica gel (petroleum ether: Et_2O = 2:1), affording 247 mg (72%) of **9a** as a white crystalline product. Mp = 138−140 °C; $[\alpha]^{24}_D$ −16.8 (*c* 1.00, $CHCl_3$); IR: 3600, 3460 cm^{-1}; MS (EI) *m/z* 291 (M^+), 200, 100, 57; ^1H NMR (200 MHz) δ 1.31 (s, 9H), 2.15−2.40 (m, 2H), 2.50 (bs, 1H), 2.70−2.80 (m, 1H), 2.91 (dd, 1H, J = 14.1, 4.2 Hz), 3.60−3.71 (m, 1H), 3.73−3.85 (m, 1H), 4.62 (d, 1H, J = 8.2 Hz), 5.10−5.20 (m, 2H), 5.75−5.90 (m, 1H), 7.10−7.30 (m, 5H); ^{13}C NMR (75.46 MHz) δ 28.2, 35.3, 38.4 55.8, 72.7 79.5, 118.2 126.3 128.3, 129.3, 134.7 138.1, 156.0. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.06; H, 8.65; N, 4.81. Found: C, 70.01; H, 8.61; N, 4.79. MTPA ester of alcohol **9a:** (*R*)−(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (50 mg, 0.19 mmol) was added to a solution of **9a** (20 mg, 0.069 mmol) in CH_2Cl_2 (3 mL) and DIMAP (18 mg, 0.14 mmol). The solution was stirred at room temperature for 36 h, diluted with 2 mL of CH_2Cl_2, and washed with saturated aqueous NH_4Cl. The water phase was extracted three times with Et_2O (3 × 10 mL) and dried over $MgSO_4$. Purification with preparative silica gel plates of the crude (CH_2Cl_2:petroleum ether = 1:1) afforded 32 mg (97%) of (*R*)-MPTA ester of **9a** as a pale yellow oil. ^1H NMR (300 MHz) δ: 1.30 (s, 9H), 2.18 (dd, J = 14.3, 10.4 Hz, 1H), 2.33−2.54 (m, 2H), 2.77 (dd, 1H, J = 14.3, 4.1 Hz), 3.58 (s, 3H), 3.90−4.12 (m, 2H), 5.05−5.18 (m, 2H), 5.35−5.45 (m, 1H), 5.68−5.85 (m, 1H), 6.90−7.00 (m, 2H), 7.10−7.30 (m, 3H), 7.35−7.48 (m, 3H), 7.52−7.62 (m, 2H).

(28) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (b) Harwood: L. M.; Moodie, C. J. *Organocopper Reagents*; Taylor, J. K., Ed.; Oxford University Press: New York, 1994; pp 260−261.

(2*S*,3*S*)-2-Amino-1-phenyl-5-hexen-3-ol (10a). A solution of **9a** (110 mg, 0.38 mmol) in 4 N HCl/dioxane (2/1) solution (12 mL) was stirred under Ar atmosphere for 1 h at room temperature and concentrated in vacuo. The solution was adjusted to pH = 9 with NH_4OH, and extracted three times with EtOAc. The organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo giving 62 mg (85%) of pure **10a** as a thick oil. $[\alpha]^{24}_D$ +31.2 (*c* 1.00, MeOH); MS (EI) *m*/*z* 191 (M^+), 176, 150, 120, 91; ^{1}H NMR (200 MHz) δ 1.55−2.20 (bs, 3H), 2.25−2.55 (m, 3H), 2.85−3.20 (m, 2H), 3.50−3.70 (bs, 1H), 5.05−5.25 (m, 2H), 5.80−6.00 (m, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR (75.46 MHz) δ 37.2, 38.2, 56.2, 73.1, 117.7, 126.4, 128.5, 129.2, 135.1, 139.2.

(4*S*,5*S*)-4-Benzyl-5-(1-propenyl)-1,3-oxazolidin-2-one (11a). To 60 mg (0.32 mmol) of **10a** in THF (1.6 mL) were added carbonyldiimidazole (73 mg, 0.45 mmol) and a catalytic amount of DMAP (5.0 mg, 0.04 mmol, 12% mol) at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc, and the organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification with preparative silica gel plates (petroleum ether:EtOAc = 2:1) afforded 65 mg (93%) of **11a** as a pale yellow oil. IR: 3480, 1750 cm^{-1}; MS (EI) *m*/*z* 217 (M^+), 175, 126, 91; ^{1}H NMR (200 MHz) δ 2.35−2.70 (m, 3H), 2.80−3.00 (m, 1H), 3.90−4.05 (m, 1H), 4.60−4.75 (m, 1H), 5.15−5.25 (m, 2H), 5.65 (bs, 1H), 5.70−5.90 (m, 1H), 7.00−7.35 (m, 5H); ^{13}C NMR (75.46 MHz) δ 33.6, 36.2, 56.6, 78.8, 118.6, 127.2, 128.9, 129.1, 132.4, 136.5, 158.3.

(2*S*,3*R*)-1-Phenyl-2-[*N*-(*tert*-butoxycarbonyl)amino]-5-hexen-3-ol (9b). The title compound was obtained as previously described for **9a**, starting from **7b** (250 mg, 0.59 mmol) in THF (8 mL) with TBAF (0.65 mL, 0.65 mmol). Column chromatography on silica gel (petroleum ether:Et_2O = 4:1) gave 118 mg (69%) of **9b** as an oil. $[\alpha]^{24}_D$ −22.3 (*c* 1.00, $CHCl_3$); IR: 3600, 3470 cm^{-1}; MS (EI) *m*/*z* 291 (M^+), 200, 100, 57; ^{1}H NMR (200 MHz) δ 1.35 (s, 9H), 2.15−2.55 (m, 3H), 2.75−2.90 (m, 2H), 3.53 (td, 1H, *J* = 6.9, 1.9 Hz), 3.70 (bq, 1H, *J* = 8.3 Hz), 4.90 (d, 1H, *J* = 8.8 Hz), 5.03−5.10 (m, 2H), 5.60−5.80 (m, 1H), 7.10−7.30 (m, 5H); ^{13}C NMR (75.46 MHz) δ 28.3, 38.8, 39.3, 55.2, 70.1, 79.3, 118.4, 126.3, 128.4, 129.32, 134.4, 138.4, 156.0. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.06; H, 8.65; N, 4.81. Found: C, 70.04; H, 8.63; N, 4.80. MTPA ester of alcohol **9b**: prepared as described for compound **9a**, starting from **9b** (26 mg, 0.089 mmol), (*R*)−(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (50 mg, 0.19 mmol) and DIMAP (21 mg, 0.17 mmol) in CH_2Cl_2 (3 mL). Purification with preparative silica gel plates of the crude (CH_2Cl_2:petroleum ether = 1:1) afforded 40 mg (94%) of (*R*)-MPTA ester of **9b** as a pale yellow oil. ^{1}H NMR (300 MHz) δ 1.30 (s, 9H), 2.30 (dd, *J* = 14.0, 9.1 Hz, 1H), 2.30−2.60 (m, 2H), 2.90 (dd, 1H, *J* = 14.0, 4.9 Hz), 3.60 (s, 3H), 3.85−4.18 (m, 2H), 5.00−5.20 (m, 2H), 5.22−5.35 (m, 1H), 5.60−5.82 (m, 1H), 6.80−6.90 (m, 2H), 7.10−7.50 (m, 6H), 7.50−7.70 (m, 2H).

(2*S*,3*R*)-2-Amino-1-phenyl-5-hexen-3-ol (10b). The title compound was prepared as described for **10a**, using **9b** (100 mg, 0.34 mmol) in 4 N HCl/dioxane (2/1) solution (15 mL). After the standard workup, 59 mg (90%) of **10b** were obtained as a thick oil. $[\alpha]^{24}_D$ −20.3 (*c* 1.00, MeOH); MS (EI) *m*/*z* 191 (M^+), 176, 150, 120, 100, 91, 77; ^{1}H NMR (200 MHz) δ 1.70−2.20 (bs, 3H), 2.40 (d, 2H, *J* = 6.2 Hz), 2.56 (dd, 1H, *J* = 9.4, 4.2 Hz), 2.80−3.05 (bs, 2H), 3.45 (bs, 1H), 5.05−5.20 (m, 2H), 5.75−5.95 (m, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR (75.46 MHz) δ 39.1, 41.1, 56.0, 72.4, 117.5, 126.4, 128.6, 129.2, 134.8, 138.6.

(4*S*,5*R*)-4-Benzyl-5(1-propenyl)-1,3-oxazolidin-2-one (11b). The title compound was prepared as described for **11a**, using **10b** (54 mg, 0.28 mmol), CDI (66 mg, 0.41 mmol), DMAP (4 mg, 0.03 mmol, 12%), and THF (1.5 mL). Purification with silica gel plates (petroleum ether:EtOAc = 2:1) gave 58 mg (95%) of **11b** as a pale yellow oil. IR: 3480, 1750 cm^{-1}; MS (EI) *m*/*z* 217 (M^+), 175, 126, 91; ^{1}H NMR (300 MHz) δ 2.20−2.40 (m, 2H), 2.80 (d, 2H, *J* = 7.4 Hz), 3.70 (q, 1H, *J* = 6.0 Hz), 4.32 (q, 1H, *J* = 5.1 Hz), 5.05−5.20 (m, 2H), 5.60−5.95 (m + bs, 2H), 7.05−7.35 (m, 5H); ^{13}C NMR (75.46 MHz) δ 38.5, 41.6, 58.1, 80.8, 119.4, 121.9, 127.2, 128.9, 129.0, 131.2, 158.6.

Sc(OTf)$_3$-Catalyzed Allylation of 6. The reaction was performed starting from **6** (1.69 g, 4.8 mmol) in CH_2Cl_2 (40 mL), tetraallyltin (0.58 mL, 679 mg, 2.4 mmol), and Sc(OTf)$_3$ (165 mg, 0.336 mmol) in CH_2Cl_2 (64 mL) under the same conditions used in the reaction of **5**. ^{1}H NMR spectrum of the crude showed the presence of a single diastereoisomer which was purified by column chromatography on silica gel (petroleum ether:Et_2O = 6:1) to give 1.13 g (60%) of pure **(4*R*,5*S*,6*S*)-5-[*N*-(*tert*-butoxycarbonyl)amino]-4-[dimethyl(phenyl)silyl]-6-methyl-1-octen-4-ol (8)** as a pale yellow oil. $[\alpha]^{24}_D$ −7.00 (*c* 2.15, $CHCl_3$); IR: 3600, 3460, 1700, 1240 cm^{-1}; MS (EI) *m*/*z* 391 (M^+), 274, 245, 186, 135, 86, 57; ^{1}H NMR (300 MHz) δ 0.381 (s, 3H), 0.406 (s, 3H), 0.55 (t, 3H, *J* = 7.0 Hz), 0.75−0.90 (m, 5H), 1.39 (s, 9H), 1.60−1.90 (m, 2H), 2.24 (dd, 1H, *J* = 13.9, 8.2 Hz), 2.42 (dd, 1H, *J* = 13.9, 7.2 Hz), 3.66 (dd, 1H, *J* = 10.2, 2.1 Hz), 4.68 (d, 1H, *J* = 10.2 Hz), 4.90−5.10 (m, 2H), 5.70−5.90 (m, 1H), 7.25−7.40 (m, 3H), 7.55−7.65 (m, 2H); ^{13}C NMR (75.46 MHz) δ −3.5, −3.4, 11.3, 18.2, 23.5, 28.3, 37.9, 42.6, 59.4, 73.6, 78.8, 118.9, 127.7, 129.1, 133.5, 134.6, 137.5, 154.6. Anal. Calcd for $C_{22}H_{37}NO_3Si$: C, 67.48; H, 9.53; N, 3.58. Found: C, 67.45; H, 9.50; N, 3.56.

Indium-Mediated Allylation of 6. The reaction was performed as described for **5**, starting from **6** (349 mg, 1.0 mmol), allyl bromide (0.20 mL, 2.34 mmol), and In (126 mg, 1.1 mmol) in 3 mL of THF. Column chromatography on silica gel gave 371 mg of **8** (95%). When the same reaction was carried out in THF/H_2O (2:1) as a solvent, a 53% yield was obtained in 12 h.

(4*S*,5*S*,6*S*)-6-Methyl-5-[*N*-(*tert*-butoxycarbonyl)amino]-1-octen-4-ol (12). This compound was prepared with the same procedure used for **9a** starting from **8** (1.12 g, 2.86 mmol) in THF (48 mL) and 3.18 mL (3.18 mmol) of a 1.0 M solution of TBAF in THF. ^{1}H and ^{13}C NMR spectrum of the crude showed the presence of a single diastereoisomer. Subsequent purification by column chromatography on silica gel (petroleum ether:Et_2O = 3:1) gave 680 mg (92%) of pure **12** as a white solid. Mp = 117−119 °C; $[\alpha]^{24}_D$ +34.2 (*c* 1.40, MeOH); IR: 3600, 3470, 1760 cm^{-1}; MS (EI) *m*/*z* 257 (M^+), 200, 186, 130, 86, 57; ^{1}H NMR (300 MHz) δ 0.75−0.90 (m, 6H), 0.95−1.20 (m, 2H), 1.40 (s, 9H), 1.41−1.60 (m, 1H), 2.00 (bs, 1H), 2.10−2.38 (m, 2H), 3.10−3.25 (m, 1H), 3.70−3.83 (m, 1H), 4.80 (d, 1H, *J* = 9.9 Hz), 5.05−5.20 (m, 2H), 5.70−5.90 (m, 1H); ^{13}C NMR (75.46 MHz) δ 11.3, 15.8, 25.5, 28.3, 36.6, 39.7, 57.9, 69.6, 78.9, 118.4, 134.7, 156.4. Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.32; H, 10.58; N, 5.44. Found: C, 65.2; H, 10.55; N, 5.41.

(4*S*,5*S*,6*S*)-5-Amino-6-methyl-1-octen-4-ol (13). The title compound was prepared as for **10a**, using **12** (108 mg, 0.42 mmol), in 4 N HCl/dioxane (2/1) solution (15 mL). After the usual workup, 53 mg (80%) of **13** was obtained as a pale yellow oil. $[\alpha]^{24}_D$ +6.5 (*c* 1.00, MeOH), MS (EI) *m*/*z* 157 (M^+), 116, 100, 86; ^{1}H NMR (200 MHz) δ 0.75-1.00 (m, 8H), 1.20 (s, 1H), 1.30-1.50 (m, 3H), 1.85-2.50 (m, 3H), 3.45-3.55 (m, 1H), 4.95-5.15 (m, 2H), 5.75−5.95 (m, 1H); ^{13}C NMR (75.46 MHz) δ 11.4, 14.0, 24.7, 29.7, 39.7, 60.8, 78.8, 119.5, 131.5.

***(4*S*,5*S*)-5-(1-Propenyl)-4-[2(*S*)]-methylpropyl]-1,3-oxazolidin-2-one (14).** The title compound was synthesized according to the procedure reported for **11a**, starting from **13** (30 mg, 0.19 mmol), CDI (42 mg, 0.26 mmol), and DMAP (3.0 mg, 0.025 mmol). Purification with preparative silica gel plates (petroleum ether:AcOEt = 4:1) gave 22 mg (63%) of **14** as a pale yellow oil. MS (EI) *m*/*z* 183 (M^+), 142, 126, 57; ^{1}H NMR (200 MHz) δ 0.70−0.90 (m, 6H), 1.00−1.50 (m, 3H), 2.30−2.40 (m, 2H), 3.30 (t, 1H, *J* = 4.8 Hz), 4.20−4.35 (m, 1H), 5.00−5.20 (m, 2H), 5.60−5.90 (m, 2H); ^{13}C NMR (75.46 MHz) δ 11.1, 14.0, 24.7, 38.9, 39.7, 60.9, 78.8, 119.5, 131.5, 156.8.

Ethyl (3*R*,4*S*)-4-[*N*-(*tert*-Butoxycarbonyl)amino]-3-[dimethyl(phenyl)silyl]-3-hydroxy-5-phenylpentanoate (15). To a solution of **5** (1.32 g, 3.45 mmol) and *tert*-butyl(dimethyl)silyl 1-ethoxyvinyl ether (836 mg, 4.14 mmol) in CH_2Cl_2 (7.0 mL) was added dropwise $BF_3{\cdot}Et_2O$ (0.49 mL, 3.85 mmol) at −78 °C under Ar atmosphere. After being stirred for 48 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated in vacuo. ^{1}H NMR spectrum of the crude showed the presence of two diastereoisomers **15a**,**b** in a 95:5 ratio. This ratio was maintained after purification by column chromatography on silica gel (petroleum ether:Et_2O = 5:1) which gave 991 mg (61%) of **15a** and **15b**. **15a**: MS (EI) *m*/*z* 471 (M^+), 398, 370, 354, 276, 164, 135, 120, 91; ^{1}H NMR (200 MHz) δ 0.40 (s, 3H), 0.50 (s, 3H), 1.10−1.30 (m, 12H), 2.50−2.65 (m, 3H), 2.96 (dd, 1H, *J* = 13.7, 3.1 Hz), 3.90−4.10 (m, 3H), 4.45 (bd, 1H, *J* = 11.1 Hz), 4.73 (s, 1H), 6.90−7.70 (m, 10H); ^{13}C

NMR (75.46 MHz) δ −4.4, −3.7, 13.94, 28.1, 37.9, 38.8, 58.2, 60.8, 70.3, 78.9, 126.1, 127.9, 128.1, 129.2, 129.5, 134.6, 136.4, 138.6, 155.4, 174.5.

A mixture of **15a** and **15b** was reacted with TBAF (2.3 mL, 2.3 mmol, 1.1 equiv) in THF (30 mL) for 24 h affording two stereoisomers in a 95:5 ratio. Purification by column chromatography on silica gel (petroleum ether:Et_2O = 6:1) gave 423 mg (60%) of **ethyl (3*S*,4*S*)-4-[*N*-(*tert*-butoxycarbonyl)amino]-3-hydroxy-5-phenylpentanoate (16a)** and 22 mg (3%) of **ethyl (3*R*,4*S*)-4-[*N*-(*tert*-butoxycarbonyl)amino]-3-hydroxy-5 phenylpentanoate (16b)**, whose spectral data were consistent with those reported in the literature.[24a−c]

(16a): $[\alpha]^{20}_D$ −36.3 (*c* 1.0, MeOH); ^{1}H NMR (200 MHz) δ: 1.24 (t, J = 7.0 Hz, 3H), 1.41 (s, 9H), 2.37 (dd, J = 16.8, 2.6 Hz, 1H), 2.59 (dd, J = 16.8, 9.9 Hz, 1H), 2.91 (d, J = 7.7 Hz, 2H), 3.46 (bd, J = 2.6 Hz,1H), 3.70−3.75 (m, 1H), 3.91−3.98 (m, 1H), 4.13 (q, J = 7.0 Hz, 2H), 4.90−4.95 (m, 1H), 7−10−7.35 (m, 5H).

(16b): $[\alpha]^{20}$ −14.4 (*c* 1.0 MeOH); ^{1}H NMR (200 MHz) δ: δ: 1.29 (t, J = 7.0 Hz, 3H), 1.34 (s, 9H), 2.41−2.64 (m, 2H), 2.80−3.00 (m, 2H), 3.59 (bs, 1H), 3.86 (bs, 1H), 3.99 (m, 1H), 4.19 (q, J = 7.0 Hz, 2H), 4.50−4.60 (m, 1H), 7−15−7.45 (m, 5H).

Ethyl (3*R*,4*S*,5*S*)-4-[*N*-(*tert*-Butoxycarbonyl)amino]-3-[dimethyl(phenyl)silyl]-3-hydroxy-5-methylheptanoate (17). The title compound was prepared as described for **15**, starting from **6** (385 mg, 1.1 mmol), *O*-ethyl-*O*-*tert*-butyldimethylsilyl ketene acetal (244 mg, 1.2 mmol) in CH_2Cl_2 (2.0 mL), and BF_3·Et_2O (0.155 mL, 1.23 mmol). Column chromatography on silica gel of the crude (petroleum ether:Et_2O = 15:1) afforded 322 mg (67%) of **17** as a pale yellow oil. $[\alpha]^{24}_D$ −6.76 (*c* 0.94, $CHCl_3$); IR: 3580, 3420; 1250 cm^{-1}; MS (EI) *m*/*z* 437 (M^+), 320, 291, 251, 157, 57; ^{1}H NMR (300 MHz) δ 0.36 (s, 3H), 0.40 (s, 3H), 0.50−0.85 (m, 6H), 1.15 (t, 3H, J = 6.7 Hz), 1.40−1.80 (m, 12H), 2.45 (s, 2H), 3.45 (d, 1H, J = 11.2 Hz), 3.92 (q, 2H, J = 6.7 Hz), 4.60 (bs, 1H), 4.83 (d, 1H, J = 11.2 Hz), 7.30−7.65 (m, 5H); ^{13}C NMR (75.46 MHz) δ −4.0, −4.1, 11.3, 13.9, 18.1, 23.3, 28.3, 38.1, 38.4, 60.7, 60.8, 72.6, 78.9, 127.7, 129.3, 134.5, 136.8, 156.4, 175.3. Anal. Calcd for $C_{23}H_{39}NO_5Si$: C, 68.10; H, 9.70; N, 3.46. Found: C, 68.01; H, 9.65; N, 3.38.

Ethyl (3S,4*S*,5*S*)-4-[*N*-(*tert*-Butoxycarbonyl)amino]-3-hydroxy-5-methylheptanoate (18). The title compound was prepared as described for **16**, using **17** (190 mg, 0.43 mmol) and TBAF (0.47 mL, 0.47 mmol) in THF (8 mL). Purification with preparative silica gel plates gave 85 mg (65%) of **18**, whose spectral data well matched[24d,e] with those reported in the literature. **(18):** $[\alpha]^{24}_D$ +26.7 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz) δ: 0.87 (t, J = 7.0 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.43 (s, 9H), 0.70−1.90 (m, 3H), 2.50−2.58 (m, 2H), 2.70 (brs, 1H), 3.25−3.35 (m, 1H), 4.21 (q, J = 7.0 Hz, 2H), 3.90−4.42 (m, 1H), 4.81 (d, J = 9.3 Hz, 1H).

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