Silylcupration of (*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine: A Stereoselective Approach to the Synthesis of γ-Silylated Saturated and Unsaturated α-Amino Acids

Gianna Reginato,* Alessandro Mordini, Michela Valacchi, and Elena Grandini

Centro CNR Composti Eterociclici, Dipartimento di Chimica Organica "U. Schiff", via G. Capponi 9, I-50121 Firenze, Italy

Received August 10, 1999

Enantioselective synthesis of γ-silylated amino acids is reported, using a four-step procedure based on the silylcupration of ethynyloxazolidine **2**. Silylcuprates **6a**−**c** are highlighted as useful reagents to be employed with enantiomerically enriched substrates. Vinylsilanes **5** are easily prepared and highlighted as useful intermediates to yield the final compounds after reduction, opening of the oxazolidine ring, and oxidation. Moreover, β,γ-unsaturated amino acids are obtained as very interesting vinylglycine derivatives. The capability of silicon-containing amino acids to be incorporated into dipeptides is also shown.

Introduction

The biological importance of natural and unnatural α-amino acids has increasingly attracted the attention for the search of new enantioselective synthetic routes to these compounds.[1−4] An interesting class of unnatural amino acids are those which contain silicon, trialkylsilyl chains being known to have hydrophobic properties which might be relevant for biological activity.[5,6] For this reason they can be used as suitable substitutes of natural lipophilic amino acids, or as replacements in naturally occurring peptides. This fact can be responsible for enhancing the biological activity and proteolytic stability of the modified peptide, as has already been observed when β-trimethysilylalanine was employed as a *bioisostere* for phenylalanine in the search for stable renin inhibitors.[7] Moreover, because of the rich reactivity known for organosilanes,[8] coupled with the growing importance of amino acids as chiral synthons,[9] silylated amino acids can be considered as useful optically active starting materials for a variety of synthetic applications.

Despite this interest only a few reports on the synthesis of these compounds are known: some trialkylsilylalanine derivatives have been prepared, in both racemic and enantiomerically enriched form,[10−13] but these are, to our knowledge, the only examples of silicon-containing amino acids which have been synthesized so far.

We have recently reported that the addition of (tributylstannyl)cuprate **1** to (*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine (**2**) is a very efficient and mild procedure to obtain γ-substituted amino acid precursors. Substrate **2** can be readily prepared,[14−16] with high enantiomeric purity, from naturally occurring L-serine, and used as an ethynylglycine synthon. The oxazolidine moiety is widely employed as a synthetic equivalent[1] of α-amino acids, and the presence of an unsaturated lateral chain[14,15,17,18] has been exploited to obtain precursors to ethynyl- and vinylglycine derivatives. For example, addition of **1** to **2**[19,20] afforded, regio- and stereoselectively, the corresponding γ-stannylated (*E*)-ethenyloxazolidine **3**, a useful intermediate which was subsequently coupled with electrophiles under Pd catalysis[21] to give the corresponding γ-substituted amino acids precursors **4** (Scheme 1). One of the most remarkable features of this protocol is that the resulting compounds showed no loss of stereochemical information, confirming metallocuprates as suitable reagents to be used on enantiomerically enriched compounds.[22,10]

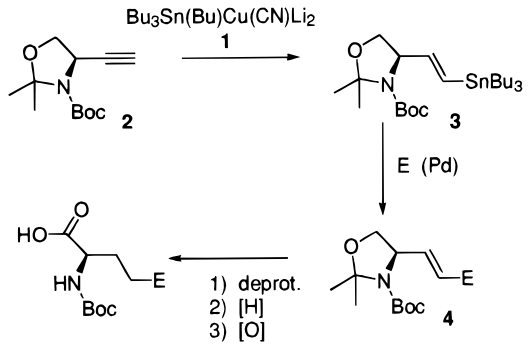
In view of these results we envisaged ethynylglycine **2** as a useful substrate for the synthesis of vinylsilanes

* To whom correspondence should be addressed. Phone: +39 055 2757609. Fax: +39 055 2476964. E-mail: reginato@cesce.fi.cnr.it.

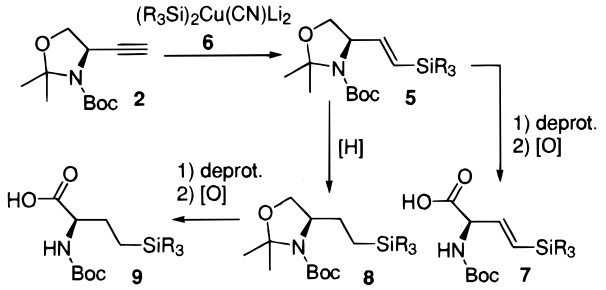
(1) Williams, R. M. *Synthesis of optically active α-amino acids*; Pergamon Press: New York, 1989; Vol. 7.
(2) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360.
(3) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 12789.
(4) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825.
(5) Tacke, R.; Linoh, H. *The Chemistry of Organosilicon Compounds*; John Wiley & Sons: New York, 1989.
(6) Tacke, R. *Organosilicon and Bioorganosilicon Chemistry; Structure, Bonding, Reactivity and Synthetic Application*; John Wiley & Sons: New York, 1985.
(7) Weidman, B. *Chimia* **1992**, *46*, 312.
(8) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.
(9) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; John Wiley & Sons: New York, 1987.
(10) Sibi, M. P.; Harris, B. J.; Shay, J. J.; Hajra, S. *Tetrahedron* **1998**, *54*, 7221.
(11) Walkup, R. D.; Cole, D. C. *J. Org. Chem.* **1995**, *60*, 2630.
(12) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.
(13) Smith, R. J.; Bratovanov, S.; Bienz, S. *Tetrahedron* **1997**, *53*, 13695.
(14) Meffre, P.; Gauzy, L.; Perdigues, C.; Desanges-Leveque, F.; Branquet, E.; Durand, P.; Le Goffic, F. *Tetrahedron Lett.* **1995**, *36*, 877.
(15) Meffre, P.; Gauzy, L.; Branquet, E.; Durand, P.; Goffic, F. L. *Tetrahedron* **1996**, *52*, 11215.
(16) Reginato, G.; Mordini, A.; Degl'Innocenti, A.; Caracciolo, M. *Tetrahedron Lett.* **1995**, *36*, 8275.
(17) Crisp, G. T.; Jiang, Y. L.; Pullman, P. P.; Savi, C. D. *Tetrahedron* **1997**, *53*, 17489.
(18) Cameron, S.; Khambay, B. P. S. *Tetrahedron Lett.* **1998**, *39*, 1987.
(19) Reginato, G.; Mordini, A.; Caracciolo, M. *J. Org. Chem.* **1997**, *62*, 6187−6192.
(20) Reginato, G.; Mordini, A.; Degl'Innocenti, A.; Manganiello, S.; Capperucci, A.; Poli, G. *Tetrahedron* **1998**, *54*, 10227.
(21) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(22) Reginato, G.; Mordini, A.; Messina, F.; Degl'Innocenti, A.; Poli, G. *Tetrahedron* **1996**, *52*, 10985.

10.1021/jo991272r CCC: $18.00
Published on Web 11/19/1999

Scheme 1



Scheme 2



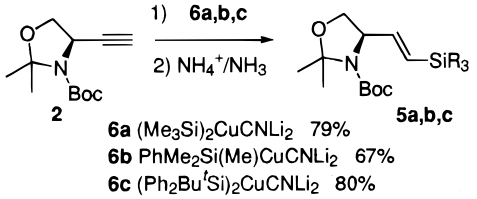
5 through silylcupration (Scheme 2). These intermediates, after reduction of the double bond, hydrolytic removal of the acetonide protecting group and oxidation, led to a new class of silylated amino acids **9**, bearing different trialkylsilyl substituents at the γ-position of the lateral chain.

The current approach would also offer the opportunity of obtaining β,γ-unsaturated amino acids **7**. Unsaturated amino acids display interesting biological properties,[23−25] and some methods have been described for the preparation of these products,[26] but most suffer from either poor control of double bond geometry or variable enantiomeric purity. Wittig condensation of phosphorus ylides with the Garner aldehyde, followed by deprotection and oxidation of the corresponding unsaturated amino alcohol, has been shown to be a practical way for preparing chiral β,γ-unsaturated amino acids with the defined double-bond geometry. The most challenging step in this procedure is the oxidation of the unsaturated amino alcohol, and we reasoned that a trialkylsilyl group could be a suitable substituent, promoting a successful oxidation of the amino alcohol derived from **5**.

Here we report the full experimental details to obtain saturated and unsaturated silicon-containing amino acids **9** and **7**, respectively. Vinylsilanes **5**, easily obtainable through addition of different silylcuprates **6** to **2**, are highlighted as useful intermediates. We also report some preliminary results which demonstrate the capability of our silylated amino acids to be incorporated into dipeptides, following the typical coupling and deprotection steps associated with peptide synthesis.

Some of the results described herein have been the subject of a preliminary communication.[27]

Scheme 3



Results and Discussion

Synthesis of Vinylsilanes 5. Trimethylsilylcyanocuprate **6a** was found to add efficiently to ethynyloxazolidine **2** at low temperature, affording, after hydrolytic workup, the corresponding γ-silylated (*E*)-ethenyloxazolidine **5a** in a regio- and syn stereoselective manner (Scheme 3). Remarkably, only one isomer was detected, as determined by ^{1}H NMR analysis of the crude mixture, the double-bond configuration being easily confirmed from the 18.3 Hz coupling for the vinyl protons, in good agreement with the assigned *E* geometry of **5a**.

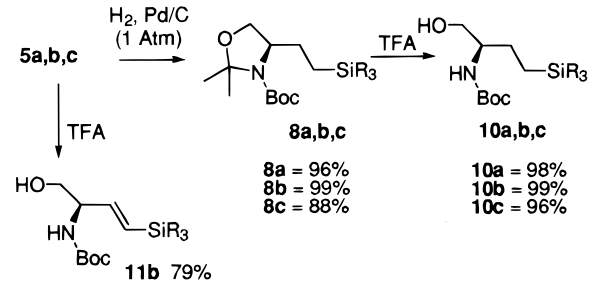
Two other silylcuprates (**6b**,**c**) have also been examined. Dimethylphenylcyanocuprate **6b** was chosen for introducing a dimethylphenylsilyl group which, although endowing vinylsilanes with a similar reactivity, has the advantage that it can be converted, if required, into a hydroxyl group.[28] A new procedure for copper-catalyzed silylcupration of terminal alkynes has been recently reported;[29] in this case a mixed species, $(PhMe_2Si)(Me)Cu(CN)Li_2$ (**6b**), is generated from a mixed zincate, $PhMe_2SiZnMe_2Li$, and 3 mol % $Me_2Cu(CN)Li_2$. Most notably, the process minimizes the amount of silyl ligand involved and requires only small percentages of CuCN and is therefore particularly appealing for large scale reactions. We have successfully applied this procedure to the synthesis of vinylsilane **5b**, which was obtained selectively on a multigram scale. $(tert\text{-}Bu)Ph_2SiCu(CN)Li_2$ (**6c**) was then chosen to introduce a hindered silyl group which could impart useful differences[30] to the chemical behavior of our target compound; once again, a clean addition leading to **5c** was observed.

In all the examined cases, no starting material was recovered in the final crude mixture, and vinylsilanes **5a**−**c** were isolated after chromatographic purification in good yields.

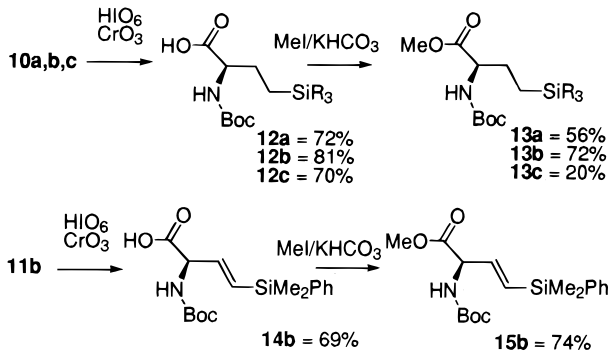
Synthesis of Silylated Amino Alcohols 10 and 11b. Pure **5a**−**c** were hydrogenated with Pd catalysis to quantitatively yield the corresponding saturated oxazolidines **8a**−**c**, which were deprotected to the corresponding amino alcohols **10a**−**c** (Scheme 4). Optimal reaction conditions were found to involve carefully monitored treatment of each starting material with an excess of CF_3-COOH in MeOH at 0 °C. Unexpectedly the *t*-Boc-protective group was not removed despite the acidic conditions, and workup afforded essentially pure amino alcohols **10a**−**c**, which were employed without further purification in the subsequent oxidative step. To check the possibility of using vinylsilanes **5** as intermediates to unsaturated amino acids, compound **5b** was depro-

(23) Posner, B. L.; Flavin, M. *J. Biol. Chem.* **1972**, *56*, 4196.
(24) Rando, R. R. *Acc. Chem. Res.* **1975**, *8*, 281.
(25) Castelhano, A. L.; Plivra, D. H.; Taylor, G. J.; Hsieh, K. C.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 2734.
(26) Beaulieau, P. L.; Duceppe, J. S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196.
(27) Reginato, G.; Mordini, A.; Valacchi, M. *Tetrahedron Lett.* **1998**, *39*, 9545.
(28) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.
(29) Lipshutz, B. H.; Sclafani, J. A.; Takanami, T. *J. Am. Chem. Soc.* **1998**, *120*, 4021−4022.
(30) Barbero, A.; Cuadrado, P.; Fleming, I.; Gonzales, A. M.; Pulido, F. J.; Sanchez, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1525.

Scheme 4



Scheme 5



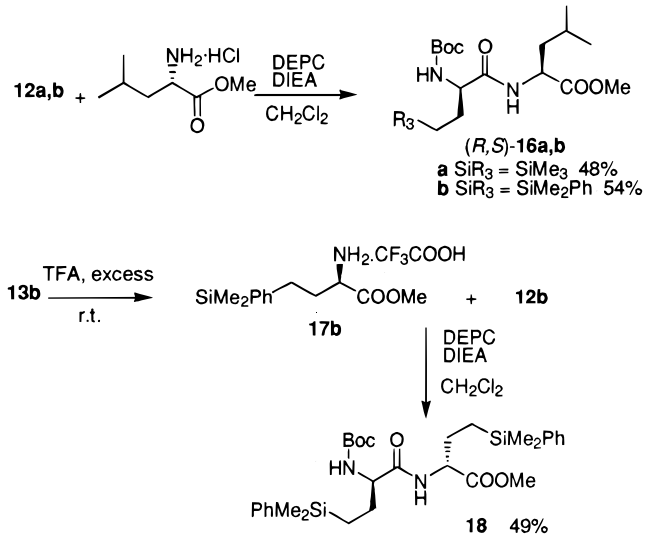
tected under the same conditions, and the corresponding unsaturated amino alcohol **11b** was obtained in good yield.

Oxidation of Amino Alcohols. Although numerous methods are reported in the literature for the direct conversion of primary alcohols to the corresponding carboxylic acids, this transformation is still a challenge especially in the presence of other functional groups. In the oxidation of our substrates we previously observed satisfactory results[27] when Jones' reagent was used applying the reverse addition procedure.[15] Recently, a new oxidative method has been reported by Zhao[31] in which the oxidation of primary alcohols to carboxylic acids is performed using periodic acid (H_5IO_6) as the stoichiometric oxidant in the presence of a catalytic amount of CrO_3. Nonracemic alcohols are oxidized without any evidence of racemization, and Cbz-protected amino alcohols are also oxidized to the corresponding Cbz-protected amino acids. This procedure worked efficiently also when applied on our silylated amino alcohols. The *t*-Boc-protective group was in fact capable of withstanding the acidic conditions required, and a rapid, clean, and high-yielding oxidation to the corresponding *t*-Boc-protected amino acids occurred as shown in Scheme 5.

It is also remarkable how the presence of a reactive double bond in **11b** did not affect the yield of oxidation, since unsaturated amino acid **14b** was recovered in satisfactory yield. The efficiency of the oxidative step in this case, which was also observed[27] when Jones' conditions were used, confirms trialkylsilyl groups as suitable substituents for obtaining vinylglycine derivatives. This is in agreement with the observation that a successful oxidation of unsaturated amino alcohols is dependent on the substituent of the terminal vinylic position, the best results being obtained in the presence of electron donor groups.[26]

(31) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. *Tetrahedron Lett.* **1998**, *39*, 5323.

Scheme 6



For characterization purposes, crude amino acids were treated with excess MeI in the presence of $KHCO_3$, and the corresponding methyl esters **13a**−**c** and **15b** were isolated in pure form after chromatography. The crude amino acids showed, however, sufficient purity for further uses.

Synthesis of Dipeptides. To demonstrate that silylated amino acids are capable of undergoing typical reactions associated with peptides synthesis, different dipeptides bearing one or two silylated residues were synthesized as shown in Scheme 6. The *t*-Boc-protected amino acids **12a**,**b** were coupled with L-leucine methyl ester using DEPC/DIEA (diethylcyanophosphonate/diisopropylethylamine) procedure to produce peptides **16a**,**b**, respectively, in 48% and 54% yields after purification. Conversely, amino ester **13b** was deprotected and the obtained trifluoroacetate **17b** coupled with Boc-protected amino acid **12b** to afford disilylated peptide **18** in good yield.

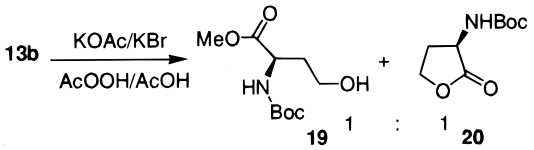
^{1}H and ^{13}C NMR analysis of the three peptides **16a**,**b** and **18** indicated the absence (within limits of detection, 5%) of peaks due to epimerization at any of the α carbons in the amino acids formed. This confirmed that during our synthetic sequence no racemization occurred and pointed out that γ-silylated amino acids are not affected by coupling and deprotection conditions usually associated with peptide synthesis.

Finally, we decided to check whether the conversion of the phenyldimethyl group into the hydroxyl group was feasible on **13b**. Among the different methods reported in the literature, bromodesilylation[28] was chosen, as the mild reaction conditions are compatible with the presence of the *t*-Boc-protective group. Addition of an excess of peracetic acid to a solution of **13b** in buffered acetic acid and potassium bromide, provided, after purification, a 1:1 mixture of Boc-protected homoserine ester **19** and lactone **20** in 64% combined yield (Scheme 7). Slow cyclization of **19** into lactone **20** occurred spontaneously in solution and was accelerated in an acidic medium.

Conclusions

A general and mild synthetic route to a novel class of silicon-containing amino acids has been developed. Vinylsilanes **5** have been highlighted as intermediates

Scheme 7



which can favorably be applied to the synthesis of silylated vinylglycine derivatives. Noteworthy, the yields of the overall process are satisfactory, since all steps can be carried out without purification of intermediates.

The ability of γ-silylated amino acids to be incorporated into peptides by solution-phase methodology has also been demonstrated, and silylated dipeptides have been synthesized.

Experimental Section

General Procedures. Ethereal extracts were dried with Na_2SO_4. The temperature of dry ice/ethanol baths is indicated as −78 °C. Reactions were monitored by TLC on SiO_2; detection was made using a $KMnO_4$ basic solution. Flash column chromatography[32] was performed using glass columns (10−50 mm wide) and SiO_2 (230−400 mesh). ^{1}H NMR were recorded at 200 or 300 MHz. ^{13}C NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$, δ 7.26 ppm for ^{1}H NMR; $CHCl_3$, δ 77.0 ppm for ^{13}C NMR). Coupling constants (J) are reported in hertz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), br s (broad singlet), br t (broad triplet), and br q (broad quartet). For those compounds which are present as slowly interconverting rotamers, NMR experiments were performed at 50 °C, and signals of the averaged spectrum are reported when possible. Mass spectra were obtained at a 70 eV ionization potential and are reported in the form *m/z* (intensity relative to base, 100). Polarimetric measurements were performed in $CHCl_3$ solution at $\lambda = 589$ nm, and the temperature is specified case by case.

Materials. Oxazolidine **2** was prepared according to the literature.[19] Starting materials are commercially available unless otherwise stated. All commercial reagents were used without further purification. THF was dried by distillation over sodium benzophenone ketyl. CH_2Cl_2 was purified by the standard procedure, dried over $CaCl_2$, and stored over 4 Å molecular sieves. DMF was distilled over $CaCl_2$, and stored over 4 Å molecular sieves. Petroleum ether, unless specified, is the 40−70 °C boiling fraction.

***tert*-Butyl 4-((1*E*)-3,3-Dimethyl-3-silabut-1-enyl)(4*R*)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5a).** Trimethylsilylcuprate **6a** was prepared according to the literature.[33] A solution of **2** (1.112 g, 4.9 mmol) in THF (2 mL) was added, and the reaction mixture was stirred at −78 °C for 30 min. The reaction was diluted with ether, and hydrolyzed with ammonium buffer. The organic layer was washed twice with brine and then dried. Evaporation of the solvent afforded 1.536 g of crude **5a**, which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 15/1). Pure **5a** (1.162 mg, 79%) was obtained as a low melting colorless solid. ^{1}H NMR (300 MHz, 55 °C): δ 6.01−5.72 (AB, J = 18.3, 6.3 Hz, 2 H), 4.36−4.22 (br m, 1 H), 4.08−3.70 (AB, J = 8.8, 6.4, 2.7 Hz, 2 H), 1.61 (s, 3 H), 1.52 (s, 3 H), 1.44 (s, 9 H), 0.08 (s, 9 H). ^{13}C NMR: δ 151.96, 144.36, 130.86, 93.95, 79.46, 68.02, 61.63, 28.30, 26.40, 23.67, −1.42. MS: *m/z* 299 (0.2), 284 (11), 73 (78), 57 (100). $[\alpha]^{25}_D = -30.7$ (c = 0.9, $CHCl_3$). Anal. Calcd for $C_{15}H_{29}NO_3Si$: C, 60.16; H, 9.76; N, 4.68. Found: C, 60.39; H, 9.72; N, 4.53.

***tert*-Butyl 4-((1*E*)-3-Methyl-3-phenyl-3-silabut-1-enyl)-(4*R*)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5b).** Dimethylphenylsilyllithium was prepared according to the literature.[34] Mixed dimethylphenylsilylzincate **6b** was prepared, and used in the presence of CuCN (0.03 equiv, 3% CuCN).[29] A precooled solution of **2** (1.66 g, 7.4 mmol) in THF (4 mL) was added, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was hydrolyzed with saturated aqueous NH_4-Cl and then extracted with ether. The organic layer was washed twice with brine and dried. Evaporation of the solvent afforded 2.75 g of crude **5b**, which was purified by flash chromatography (petroleum ether/ethyl acetate, 6/1). Pure **5** (1.81 g, 67%) was obtained as a colorless oil. ^{1}H NMR: δ 7.56−7.46 (m, 2 H), 7.36−7.30 (m, 3 H), 6.11−5.76 (AB, J = 18.8, 6.6 Hz, 2 H), 4.35−4.25 (br m, 1 H), 4.09−3.73 (AB, J = 8.8, 6.2, 2.2 Hz, 2 H), 1.60 (br s, 3 H), 1.51 (br s, 3 H), 1.38 (br s, 9 H), 0.34 (s, 6 H). ^{13}C NMR: δ 151.94, 146.18, 133.78, 128.98, 128.65, 127.94, 127.74, 94.06, 79.51, 67.99, 61.54, 28.28, 26.48, 23.67, −2.71. MS: *m/z* 346 (1), 290 (18), 135 (53), 57 (100). $[\alpha]^{26}_D = -36.8$ (c = 0.9, $CHCl_3$). Anal. Calcd for $C_{20}H_{31}NO_3Si$: C, 66.44; H, 8.64; N, 3.87. Found: C, 66.32; H, 8.67; N, 3.58.

***tert*-Butyl 4-((1*E*)-4,4-Dimethyl-3,3-diphenyl-3-silapent-1-enyl)(4*R*)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5c).** *tert*-Butyldiphenylsilylcuprate **6c** (2 equiv) was prepared according to the literature.[30] A solution of **2** (168 mg, 0.75 mmol) in THF (1 mL) was added, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was hydrolyzed with ammonium buffer at low temperature, allowed to warm to room temperature, and extracted with ether. The organic layer was washed twice with brine and then dried. Evaporation of the solvent afforded 510 mg of a crude mixture, which was purified by flash chromatography (petroleum ether/ethyl acetate, 6/1). Pure **5c** (283 mg, 80%) was obtained as a low melting white solid. ^{1}H NMR: δ 7.75−7.58 (m, 4 H), 7.42−7.30 (m, 6 H), 6.28−5.98 (AB, J = 18.6, 4.8 Hz, 2 H), 4.48−4.39 (m, 1 H), 4.11−3.75 (AB, J = 8.8 Hz, 6.2, 1.4 Hz, 2 H), 1.62 (br s, 3 H), 1.55 (br s, 3 H), 1.45 (br s, 9 H), 1.10 (s, 9 H). ^{13}C NMR: δ 151.94, 148.71, 137.48, 136.17, 129.12, 127.56, 123.50, 94.18, 79.66, 68.08, 61.29, 28.33, 27.62, 26.44, 24.87, 23.53. MS: *m/z* 408 (3), 352 (34), 276 (20), 199 (62), 164 (70), 135 (17), 83 (46), 57 (100). $[\alpha]^{23}_D = -52.0$ (c = 1.3, $CHCl_3$). Anal. Calcd for $C_{28}H_{39}NO_3Si$: C, 72,21; H, 8,44; N, 3,01. Found: C, 72.39; H, 8.47; N, 3.07.

Hydrogenation of Vinylsilanes. Compounds **5a**−**c** were dissolved in 95% ethanol, and hydrogenated (H_2, 1 atm) over a catalytic amount of Pd on carbon. The reaction was monitored by GC; after completion, the solution was filtered over Celite. Evaporation of the solvent afforded pure compounds **8**, which were employed in the following step without further purification.

***tert*-Butyl (4*R*)-4-(3,3-Dimethyl-3-silabutyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (8a).** Compound **5a** (644 mg, 2.2 mmol) was hydrogenated for 3 h, affording 625 mg (96%) of **8a**. ^{1}H NMR (300 MHz, 55 °C): δ 3.96−3.86 (m, 1 H), 3.76−3.62 (m, 1 H + 1 H), 1.79−1.62 (m, 2 H), 1.57 (br s, 3 H), 1.48−1.46 (m, 9 H + 3 H), 0.48−0.35 (m, 2 H), 0.01 (s, 9 H). ^{13}C NMR (75.45 MHz): δ 156.60, 93.65, 79.46, 66.52, 55.54, 28.43, 27.61, 25.75, 23.28, 12.90, −1.83. MS: *m/z* 286 (2), 230 (9), 73 (33), 57 (100). $[\alpha]^{20}_D = -36.1$ (c = 1.05, $CHCl_3$).

***tert*-Butyl (4*R*)-2,2-Dimethyl-4-(3-methyl-3-phenyl-3-silabutyl)-1,3-oxazolidine-3-carboxylate (8b).** Compound **5b** (1.48 g, 4.1 mmol) was hydrogenated for 6 h, affording 1.48 g (99%) of **8b**. ^{1}H NMR: δ 7.52−7.46 (m, 2 H), 7.36−7.32 (m, 3 H), 3.90 (dd, J = 8.4, 5.4 Hz, 1 H), 3.76−3.45 (m, 1 H + 1 H), 1.60−1.20 (m, 2 H + 3 H + 3 H), 1.44 (br s, 9 H), 0.90−0.60 (m, 2 H), 0.27 (s, 6 H). ^{13}C NMR (75.45 MHz): δ 156.64, 138.70, 133.48, 128.98, 127.82, 87.00, 79.58, 65.49, 55.35, 28.33, 27.39, 26.64, 25.64, 11.86, −3.27. MS: *m/z* 348 (2), 292 (10), 135 (100), 57 (100). $[\alpha]^{22}_D = -13.2$ (c = 0.7, $CHCl_3$).

***tert*-Butyl (4*R*)-4-(4,4-Dimethyl-3,3-diphenyl-3-silapentyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (8c).** Com-

(32) Still, W. C.; Ahn, M. K.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(33) Capella, L.; Degl'Innocenti, A.; Reginato, G.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1989**, *54*, 1473.

(34) Fleming, I. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; p 260.

pound **5c** (281 mg, 0.6 mmol) was dissolved in a mixture of 95% ethanol/petroleum ether (70/30) and hydrogenated for 7 h, affording 248 mg (88%) of **8c**. ^{1}H NMR: δ 7.77−7.58 (m, 4 H), 7.41−7.32 (m, 6 H), 3.99−3.69 (m, 2 H + 1 H), 1.65−1.30 (m, 2 H + 6 H), 1.47 (br s, 9 H), 1.25−0.90 (m, 2 H), 1.05 (s, 9 H). ^{13}C NMR: δ 152.13, 137.50, 135.86, 129.11, 127.70, 93.81, 79.62, 65.80, 55.71, 28.33, 27.78, 26.51, 24.65, 23.18, 20.30, 18.05. MS: *m*/*z* 354 (21), 135 (17), 57 (100). $[\alpha]^{19}_D = -30.2$ (*c* = 1.0, $CHCl_3$).

Deprotection to Amino Alcohols. A solution of **8** in MeOH was cooled to 0 °C and then treated with an excess of CF_3COOH. The reaction was monitored by TLC every 30 min; after completion, solvent was evaporated and the residue redissolved with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, then dried, and evaporated to afford pure amino alcohols **10a**−**c** and **11b**, which were oxidized without further purification.

***N*-[(1*R*)-1-(3,3-Dimethyl-3-silabutyl)-2-hydroxyethyl]-(*tert*-butoxy)carboxamide (10a).** Compound **8a** (551 mg, 1.8 mmol) was reacted for 4 h to afford, after workup, 469 mg (98%) of **10a**. ^{1}H NMR: δ 4.70−4.44 (br m, 1 H), 3.74−3.46 (m, 2 H + 1 H), 1.90 (br s, 1 H), 1.58−1.32 (m, 2H), 1.45 (s, 9 H), 0.64−0.38 (m, 2 H), 0.01 (s, 9 H). ^{13}C NMR: δ 156.69, 79.57, 65.27, 55.48, 28.33, 25.69, 12.60, −1.93. MS: *m*/*z* 230 (2), 73 (46), 57 (100). $[\alpha]^{25}_D = +9.12$ (*c* = 1.02, $CHCl_3$).

***N*-[(1*R*)-2-Hydroxy-1-(3-methyl-3-phenyl-3-silabutyl)-ethyl](*tert*-butoxy)carboxamide (10b).** Compound **8b** (1.48 g, 4.1 mmol) was reacted for 4 h to afford, after workup, 1.31 g (99%) of **10b**. ^{1}H NMR: δ 7.56−7.44 (m, 2 H), 7.38−7.31 (m, 3 H), 4.75−4.62 (br m, 1 H), 3.65−3.49 (m, 2 H + 1 H), 2.68 (br s, 1 H), 1.55−1.35 (m, 2 H), 1.44 (s, 9 H), 0.83−0.70 (m, 2 H), 0.27 (s, 6 H). ^{13}C NMR: δ 156.60, 138.70, 133.49, 128.94, 127.80, 79.55, 65.26, 55.35, 28.30, 25.60, 11.78, −3.31. MS: *m*/*z* 324 (8), 135 (100), 57 (100). $[\alpha]^{22}_D = -1.06$ (*c* = 1.3, $CHCl_3$).

***N*-[(1*R*)-1-(4,4-Dimethyl-3,3-diphenyl-3-silapentyl)-2-hydroxyethyl](*tert*-butoxy)carboxamide (10c).** Compound **8c** (248 mg, 0.5 mmol) was reacted for 5 h to afford, after workup, 217 mg (96%) of **10c**. ^{1}H NMR: δ 7.65−7.56 (m, 4 H), 7.39−7.31 (m, 6 H), 3.81−3.64 (br m, 1 H), 3.63−3.42 (m, 2 H + 1 H), 2.83 (br s, 1 H), 1.48−1.04 (m, 2 H + 2 H), 1.44 (s, 9 H), 1.03 (s, 9 H). ^{13}C NMR: δ 156.62, 137.43, 135.81, 129.05, 127.54, 79.53, 64.91, 55.55, 28.28, 27.75, 26.25, 20.25, 6.38. MS: *m*/*z* 354 (10), 135 (31), 57 (100). $[\alpha]^{20}_D = -14.8$ (*c* = 1.6, $CHCl_3$).

***N*-[1-((1*E*)-3-Methyl-3-phenyl-3-silabut-1-enyl)(1*R*)-2-hydroxyethyl](*tert*-butoxy)carboxamide (11b).** Compound **5b** (560 mg, 1.5 mmol) was reacted for 8 h to afford, after workup, 395 mg (79%) of **11b**. ^{1}H NMR: δ 6.03 (br s, 2 H), 4.27 (br s, 1H), 3.76−3.55 (AB, *J* = 11.1, 5.8, 4.2 Hz, 2 H), 2.52 (br s, 1 H), 1.44 (s, 9 H), 0.35 (s, 6 H). ^{13}C NMR: δ 156.12, 144.27, 138.15, 133.78, 129.38, 129.07, 127.80, 79.84, 65.09, 56.44, 28.26, −2.73. MS: *m*/*z* 250 (5), 234 (46), 135 (29), 57 (100). $[\alpha]^{23}_D = -5.5$ (*c* = 1.1, $CHCl_3$).

Oxidation of Amino Alcohols. A stock solution of H_5IO_6 (0.4 M, 2.5 equiv) and CrO_3 (0.5% mol) in wet acetonitrile[31] was added dropwise to a cooled solution of amino alcohols **10a**−**c** and **11b** in wet acetonitrile, over a period of 30−40 min. After completion of the addition, the reaction mixture was stirred for 30 min and monitored by TLC. The reaction was quenched with phosphate buffer, toluene added, and the organic layer separated, washed with brine/H_2O, aqueous $NaHSO_3$ (0.4 M), and brine, and then dried. Crude amino acids **12a**−**c** and **14b** were dissolved in dry DMF at room temperature, $KHCO_3$ (2 equiv) and MeI (2 equiv) were added, and the mixture was allowed to react for 24−48 h at room temperature. After completion, ethyl acetate was added, and the organic layer was washed with water and brine and then dried. Purification afforded pure amino esters **13a**−**c** and **15b**.

Methyl (2*R*)-2-[(*tert*-Butoxy)carbonylamino]-5,5-dimethyl-5-silahexanoate (13a). Compound **10a** (53 mg, 0.2 mmol) was oxidized to afford 38 mg (72% yield) of crude amino acid **12**. Esterification and purification (petroleum ether/ethyl acetate, 5/1) afforded 23 mg (40% overall yield) of **13a** as a colorless oil. ^{1}H NMR: δ 5.03 (br d, *J* = 7.6 Hz, 1 H), 4.31−4.24 (m, 1 H), 3.73 (s, 3 H), 1.79−1.62 (m, 2 H), 1.44 (s, 9 H), 0.51−0.39 (m, 2 H), −0.03 (s, 9 H). ^{13}C NMR: δ 173.31, 154.69, 79.77, 55.52, 52.13, 28.26, 27.20, 11.44, −2.02. MS: *m*/*z* 233 (1), 73 (100), 57 (100). $[\alpha]^{25}_D = -21.7$ (*c* = 1.05, $CHCl_3$). Anal. Calcd for $C_{13}H_{27}NO_4Si$: C, 53,94; H, 9,40; N, 4,84. Found: C, 53.47; H, 9.47; N, 4.92.

Methyl (2*R*)-2-[(*tert*-Butoxy)carbonylamino]-5-methyl-5-phenyl-5-silahexanoate (13b). Compound **10b** (386 mg, 1.2 mmol) was oxidized to afford 326 mg (81% yield) of crude amino acid **12b**. Esterification and purification (petroleum ether/ethyl acetate, 5/1) afforded 196 mg of **13b** (58% overall yield) as a colorless oil. ^{1}H NMR: δ 7.50−7.44 (m, 2 H), 7.36−7.33 (m, 3 H), 5.01 (br d, *J* = 7.2 Hz, 1 H), 4.34−4.24 (m, 1 H), 3.71 (s, 3 H), 1.84−1.53 (m, 2 H), 1.43 (s, 9 H), 0.91−0.65 (m, 2 H), 0.26 (s, 6 H). ^{13}C NMR: δ 173.20, 156.59, 138.23, 133.53, 129.09, 127.87, 79.86, 55.48, 52.15, 28.28, 27.15, 10.65, −3.34. MS: *m*/*z* 352 (1.6), 135 (100), 57 (90). $[\alpha]^{25}_D = -20.2$ (*c* = 2, $CHCl_3$). Anal. Calcd for $C_{18}H_{29}NO_4Si$: C, 61,50; H, 8,32; N, 3,98. Found: C, 61.47; H, 8.38; N, 3.92.

Methyl (2*R*)-2-[(*tert*-Butoxy)carbonylamino]-6,6-dimethyl-5,5-diphenyl-5-silaheptanoate (13c). Compound **10c** (166 mg, 0.4 mmol) was oxidized to afford 118 mg (70% yield) of crude amino acid **12c**. Esterification and purification (petroleum ether/ethyl acetate, 5/1) afforded 23 mg of **13c** (13% overall yield) as a colorless oil. ^{1}H NMR: δ 7.58−7.52 (m, 4 H), 7.41−7.34 (m, 6 H), 5.02 (br d, *J* = 7.8, 1 H), 4.34−4.22 (m, 1 H), 3.70 (s, 3 H), 1.66−1.54 (m, 2 H), 1.45 (s, 9 H), 1.21−1.07 (m, 2 H), 1.02 (s, 9 H). ^{13}C NMR: δ 173.01, 155.38, 135.80, 133.96, 129.17, 127.70, 79.90, 55.53, 52.12, 28.30, 27.79, 27.49, 18.10, 5.40. MS: *m*/*z* 342 (54), 239 (9), 57 (100). $[\alpha]^{21}_D = -28.7$ (*c* = 1.1, $CHCl_3$). Anal. Calcd for $C_{26}H_{37}NO_4Si$: C, 68.53; H, 8.18; N, 3.07. Found: C, 68.44; H, 8.12; N, 2.89.

Methyl (3*E*)(2*R*)-2-[(*tert*-Butoxy)carbonylamino]-5-methyl-5-phenyl-5-silahex-3-enoate (15b). Compound **11b** (177 mg, 0.55 mmol) was oxidized to afford 126 mg (69% yield) of crude amino acid **14b**. Esterification and purification (petroleum ether/ethyl acetate, 4/1) afforded 96 mg (51% overall yield) of **15b** as a colorless oil. ^{1}H NMR: δ 7.52−7.46 (m, 2 H), 7.37−7.33 (m, 3 H), 6.12 (s, 2 H), 5.20 (br d, *J* = 8.2, 1 H), 4.95 (br d, *J* = 8 Hz, 1 H), 3.76 (s, 3 H), 1.45 (s, 9 H), 0.35 (s, 6 H). ^{13}C NMR: δ 171.08, 154.97, 140.60, 137.78, 133.78, 130.28, 129.13, 127.79, 80.10, 57.35, 52.54, 28.24, −2.77. MS: *m*/*z* 249 (0.5), 234 (27), 189 (33), 135 (34), 57 (100). $[\alpha]^{21}_D = -15.3$ (*c* = 1.06, $CHCl_3$). Anal. Calcd for $C_{18}H_{27}NO_4Si$: C, 61.86; H, 7.79; N, 4.01. Found: C, 61.95; H, 7.76; N, 4.11.

Synthesis of Dipeptides 16a,b and 18. Amino alcohols were oxidized, and the crude mixture obtained after workup was dissolved in dry CH_2Cl_2 and reacted under N_2 at 0 °C. The desired hydrochloride or trifluoroacetate amino ester was added followed by DIEA (3 equiv) and DEPC (1.3 equiv). The mixture was allowed to reach rt and left to stir overnight. The reaction was then diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, and then dried. Flash chromatography yielded pure dipeptides as single diastereoisomers.

Methyl 2-{(2*R*)-2-[(*tert*-Butoxy)carbonylamino]-5,5-dimethyl-5-silahexanoylamino}(2*S*)-4-methylpentanoate (16a). Compound **10a** (341 mg, 1.3 mmol) was oxidized and the crude mixture reacted with 118 mg (0.6 mmol) of L-Leu-OMe·HCl to give after purification (petroleum ether/ethyl acetate, 3/1) 251 mg (48%) of **16a** as a colorless oil. ^{1}H NMR: δ 6.53 (br d, *J* = 8 Hz, 1 H), 5.10−4.94 (m, 1 H), 4.66−4.53 (m, 1 H), 4.12−3.98 (m, 1 H), 3.70 (s, 3 H), 1.93−1.73 (m, 1 H), 1.68−1.48 (m, 2 H + 2 H), 1.43 (s, 9 H), 0.91 (d, *J* = 4.8 Hz, 6 H), 0.47 (dd, *J* = 10.1, 7.5 Hz, 2 H), −0.04 (s, 9 H). ^{13}C NMR: δ 173.24, 171.79, 155.59, 80.06, 56.66, 52.24, 50.54, 41.41, 28.25, 26.88, 24.76, 22.80, 21.72, 11.84, −1.94. MS: *m*/*z* 331 (6), 73 (66), 57 (100). $[\alpha]^{22}_D = +3.44$ (*c* = 1.1, $CHCl_3$). Anal. Calcd for $C_{19}H_{38}N_2O_5Si$: C, 56.68; H, 9.51; N, 6.96. Found: C, 56.76; H, 9.50; N, 6.81.

Methyl 2-{(2*R*)-2-[(*tert*-Butoxy)carbonylamino]-5-methyl-5-phenyl-5-silahexanoylamino}(2*S*)-4-methylpentanoate (16b). Compound **10b** (315 mg, 1.0 mmol) was oxidized and the crude mixture reacted with 182 mg (1.0 mmol) of L-Leu-OMe·HCl to give after purification (petroleum ether/

ethyl acetate, 3/1) 232 mg (51%) of **16b** as a colorless solid (mp 60−62 °C). ^{1}H NMR: δ 7.50−7.45 (m, 2 H), 7.38−7.31 (m, 3 H), 6.42 (br d, J = 7.3 Hz, 1 H), 4.98 (br d, J = 4.4 Hz, 1 H), 4.65−4.55 (m, 1 H), 4.15−3.95 (m, 1 H), 3.70 (s, 3 H), 1.95−1.72 (m, 1 H), 1.70−1.50 (m, 2 H + 2 H), 1.43 (s, 9 H), 0.91 (d, J = 5.5 Hz, 6 H), 0.79−0.66 (m, 2 H) 0.26 (s, 6 H). ^{13}C NMR: δ 173.13, 171.61, 155.54, 138.40, 133.47, 129.01, 127.80, 80.08, 56.58, 52.21, 50.54, 41.41, 28.23, 26.81, 24.76, 22.77, 21.73, 11.13, −3.33. MS: *m*/*z* 449 (7), 393 (7), 135 (73), 57 (100). $[\alpha]^{20}_D$ = 0.0 (*c* = 1.1, $CHCl_3$). Anal. Calcd for $C_{24}H_{40}N_2O_5Si$: C, 62.03; H, 8.68; N, 6.03. Found: C, 61.72; H, 8.57; N, 5.93.

Methyl (2*R*)-2-{(2*R*)-2-[(*tert*-Butoxy)carbonylamino]-5-methyl-5-phenyl-5-silahexanoylamino}-5-methyl-5-phenyl-5-silahexanoate (18). Amino ester **13b** (130 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (4 mL) and reacted at rt with TFA (1 mL). After 15 min the solvent was evaporated to afford trifluoroacetate **17**. Crude amino acid **12b** (109 mg 0.3 mmol) was reacted with **17** to give after purification (petroleum ether/ethyl acetate, 4/1) 89 mg (49%) of **18** as an oil. ^{1}H NMR: δ 7.52−7.43 (m, 5 H), 7.37−7.32 (m, 5 H), 6.44 (br d, J = 7.6 Hz, 1 H), 4.96 (br d, J = 7.2 Hz, 1 H), 4.61−4.50 (m, 1 H), 4.06−3.98 (m, 1 H), 3.69 (s, 3 H), 1.91−1.54 (m, 4 H), 1.42 (s, 9 H), 0.81−0.62 (m, 4 H), 0.27 (s, 6 H), 0.25 (s, 6 H). ^{13}C NMR: δ 172.26, 171.54, 155.50, 138.41, 138.18, 133.45, 129.01, 127.78, 79.93, 56.67, 54.10, 52.15, 28.23, 26.79, 11.09, 10.58, −3.23, −3.28, −3.38, −3.46. MS: *m*/*z* 556 (5), 500 (4), 236 (39), 135 (100), 114 (47), 57 (39). $[\alpha]^{24}_D$ = −19.7 (*c* = 1.7, $CHCl_3$). Anal. Calcd for $C_{30}H_{46}N_2O_5Si_2$: C, 63.16; H, 8.12; N, 4.91. Found: C, 63.37; H, 8.20; N, 5.06.

Methyl (2*R*)-2-[(*tert*-Butoxy)carbonylamino]-4-hydroxybutanoate (19) and *N*-[(3*R*)-2-oxo(3,4,5-trihydrofur-3-yl)](*tert*-butoxy)carboxamide (20). Potassium bromide (42 mg, 0.4 mmol) and anhydrous potassium acetate (90 mg) were added to a stirred solution of **13b** (103 mg, 0.3 mmol) in glacial acetic acid (3 mL). Peracetic acid (0.8 mL) was then added dropwise to the mixture with ice cooling. More potassium acetate (260 mg) and peracetic acid (2.5 mL) were added to the mixture, and the resulting solution was stirred at rt overnight. After addition of ether and powdered sodium thiosulfate, the solution was filtered through Celite and evaporated. The residue was redissolved in ether, and the solution was washed with aqueous $NaHCO_3$ and brine, then dried, and evaporated to afford 122 mg of crude mixture. After purification (petroleum ether/ethyl acetate, 1/1) 18 mg of **19** (26%) and 22 mg of **20** (38%) were obtained. (**19**) ^{1}H NMR: δ 5.38 (br s, 1 H), 4.54−4.39 (m, 1 H), 3.81−3.60 (m, 2 H), 3.75 (s, 3 H), 2.73 (br s, 1 H), 2.25−1.98 (m, 2H), 1.43 (s, 9 H). ^{13}C NMR: δ 175.29, 155.44, 80.62, 65.72, 52.50, 50.21, 30.57, 28.22. MS: *m*/*z* 174 (26), 57 (55). (**20**) ^{1}H NMR: δ 5.12 (br s, 1 H), 4.47−4.16 (m, 1H + 2H), 2.77−2.67 (m, 1 H), 2.26−2.11 (m, 1H), 1.44 (s, 9 H). ^{13}C NMR: δ 175.33, 155.45, 80.64, 71.77, 65.73, 28.22, 19.10. MS: *m*/*z* 146 (22), 57 (100). $[\alpha]^{21}_D$ = −9.9 (*c* = 1.3, $CHCl_3$).

JO991272R