# Thiazole-Based Stereoselective Routes to Leucine and Phenylalanine Hydroxyethylene Dipeptide Isostere Inhibitors of Renin and HIV-1 Aspartic Protease†

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A new synthesis of hydroxyethylene dipeptide isosteres for Leu-Leu and Phe-Phe in their γ-lactone form **1a** and **1b** employing β-amino-α-hydroxy aldehydes with singly and doubly protected nitrogen has been developed. These key intermediates, which are available through the thiazole–aldehyde synthesis from L-leucine and L-phenylalanine, were converted to alkanoates by Wittig olefination and reduction of the ethylenic double bond. Lactonization and stereoselective alkylation at C-2 of the resulting lactones completed the building up of the structural framework. Overall yields were in the range 16–19% for **1a** and 22–23% for **1b**.

Aspartic proteases[1] are proteolytic enzymes with two aspartyl groups in the active site that have received increasing attention over the last two decades because of their involvement in various human diseases. This class of compounds includes the blood pressure regulating enzyme renin[2] and the virally encoded key protease[3] presiding over one of the various events through which the replication of the human immunodeficiency virus (HIV-1) takes place, i.e., the processing of the *gag* and *gag-pol* polyproteins generated inside of the infected cells.[4] The inhibition of these enzymes has thus become a strategy for treatment of hypertension[5] and the acquired immunodeficiency syndrome (AIDS).[6] On the basis of the transition state mimetic concept,[7] the replacement of the scissile amide bond in short substrate peptide analogues (peptidomimetics) with nonhydrolyzable moieties that mimicked the transistion state of the enzyme-catalyzed hydrolysis reaction[8] was quite successful. One class of potent synthetic inhibitors of aspartyl proteases that has been studied contains a dipeptide mimic known as hydroxyethylene dipeptide isostere **I**. Therefore, numerous pathways leading to the isostere unit **I** have been reported starting from disparate chiral compounds.[9] Syntheses of L-Leu-L-Leu and L-Phe-L-Phe hydroxyethylene dipeptide isosteres **Ia** and **Ib** in their lactone form **1a** and **1b** have been originally described by two research groups through totally different procedures. The 4-alkylamino lactone **1a** was obtained in 12.5% overall yield by chain elongation of L-leucinal with the lithium salt of ethyl propiolate,[10] whereas **1b** was prepared in 19% overall yield by amination of D-mannofuranose.[11] More recently, another synthesis of **1b** (23% overall yield) by reduction of an amino ketone derived from L-phenylalanine has been reported.[12] The major concern in these syntheses was the stereochemistry at the C-4-bearing hydroxyl group since the *S* configuration at this center corresponding to the *3S* configuration of statine appeared especially crucial to inhibition. Also, the control of the *R* configuration of the C-2 center was considered as well, but subsequent work by one of these groups[13] established that this stereochemistry is not essential for the inhibitory potency against HIV-protease.

Our efforts have been aimed at developing a synthetic strategy leading to both lactones **1a** and **1b** and eventually to other similar products bearing different substituents at C-2 and C-5 centers. Attention was focused on the use of chiral β-amino-α-hydroxy aldehydes **II** which were readily available from α-amino acids **III** through the thiazole-aldehyde synthesis.[14] The conversion of

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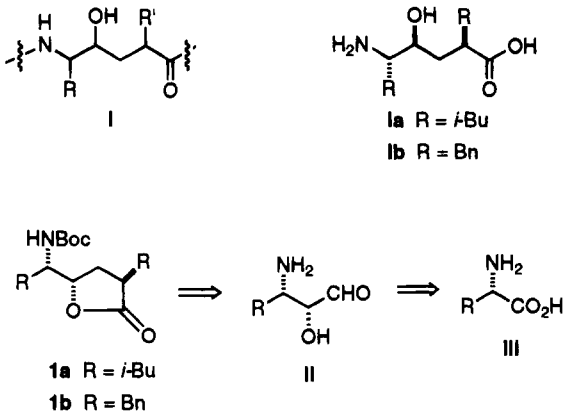
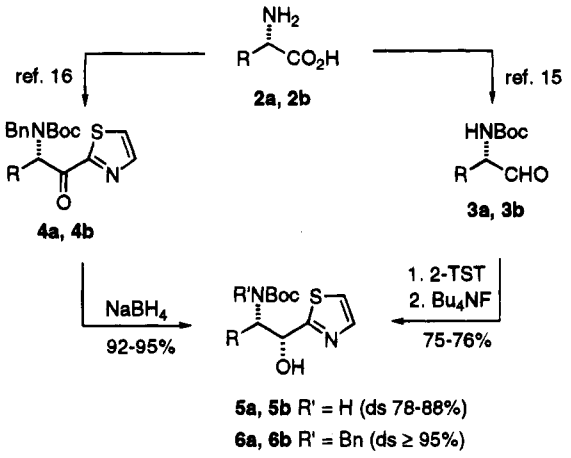
**Scheme 1**




**Scheme 2**[a]



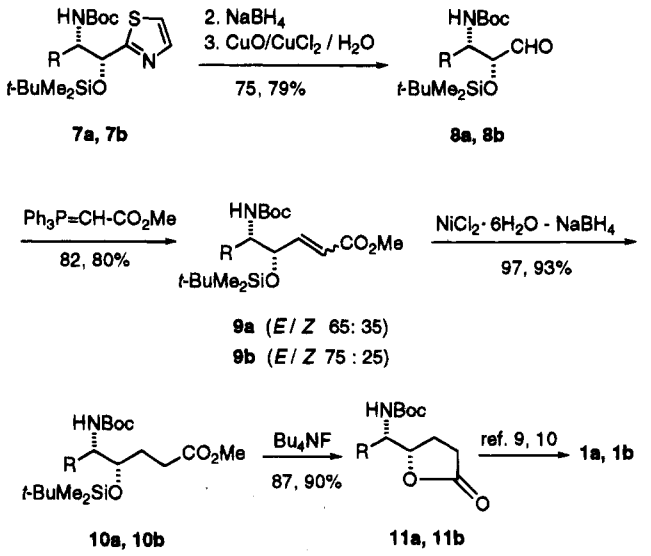

[a] 2-TST = 2-(trimethylsilyl)thiazole. Compounds **2a**–**6a**: R = *i*-Bu; yields are quoted as the first figures under the arrows. Compounds **2b**–**6b**: R = Bn; yields are quoted as the second figures under the arrows.

these aldehydes to **1** essentially requires the installation of an alkanoate unit and lactonization (Scheme 1). The execution of this synthetic plan by two complementary approaches is presented below. Partial results of this work have been previously reported.[15]

## Results and Discussion

The synthesis of β-amino-α-hydroxy aldehydes **II** from L-leucine **2a** and L-phenylalanine **2b** was secured by the ready access to their thiazole-masked equivalents **5** and **6** through two reaction sequences (Scheme 2). One involved the reduction of the α-amino acids to the *N*-monoprotected α-amino aldehydes **3a** and **3b** which were then reacted with 2-(trimethylsilyl)thiazole (2-TST) to give **5a** and **5b** as major diastereomers (amino aldehyde route).[16] The other involved the conversion of the same α-amino acids to *N,N*-diprotected 2-thiazolyl α-amino ketones **4a** and **4b** which were then reduced stereoselectively to give **6a** and **6b** as major products (amino ketone route).[17,18] With *syn* amino alcohols **5** and **6** containing a singly and doubly protected nitrogen in hand, the lactone **1** synthesis proceeded as follows.

**Scheme 3**[a,b]




[a] Compounds **7a**–**11a**: R = *i*-Bu; yields are quoted as the first figures under the arrows. [b]Compounds **7b**–**11b**: R = Bn; yields are quoted as the second figures under the arrows.

We first considered the elaboration of **5a** and **5b** since we sought the conversion of these compounds into the same ultimate precursors to **1a** and **1b** described by Kleinman[10] and Ghosh.[11] The purification of **5a** and **5b** from their *anti* diastereomers was accomplished following silylation of the crude products obtained from the addition of 2-TST to the aldehydes **3a** and **3b**. The resulting products **7a** (60% yield from **2a**) and **7b** (56% yield from **2b**) were then submitted to the one-pot thiazolyl-to-formyl unmasking sequence (*N*-methylation, reduction, hydrolysis)[19] to give the aldehydes **8a** and **8b** (Scheme 3). These compounds decomposed considerably upon column chromatography. However, they were judged by $^1$H NMR analysis to be pure enough for the continuation of the synthetic sequence.

We then turned our attention to the construction of the lactone ring. The Wittig olefination of aldehydes **8a** and **8b** with the stabilized ylide ((methoxycarbonyl)-methylene)triphenylphosphorane was carried out in toluene at room temperature. In both cases, the reaction proceeded with low *E*/*Z* selectivity, giving rise to the enoates **9a** and **9b** as a mixtures of *E* and *Z* isomers in ca. 3:1 ratio although in good overall yield (82 and 80%). Next, the reduction of the ethylenic double bond without affecting the ester group was conveniently carried out by the use of nickel boride generated in situ[20] from $NiCl_2$ hexahydrate and $NaBH_4$. Both alkanoates **10a** and **10b** were isolated in very high yields (93 and 97%) and good purity by $^1$H NMR. The hydrogenation over 10% Pd–C

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(18) It is worth mentioning here that a reversal of the diastereoselectivity can be achieved by using amino aldehydes (ref 16) and amino ketones (ref 17) with double or single protection of the amino group. This tunable stereoselectivity has been extended to the addition of 2-lithiothiazole to *N*-benzylnitrones derived from α-amino aldehydes (Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *J. Chem. Soc., Chem. Commun.* **1994**, 1731).

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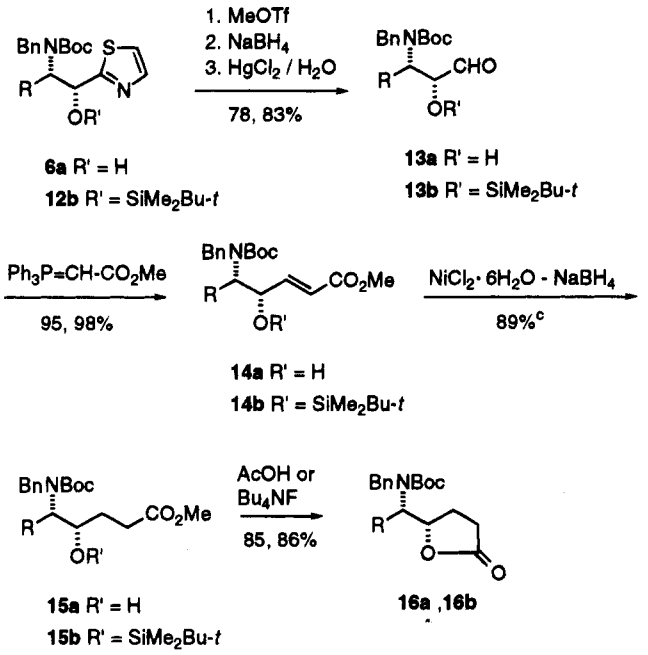
**Scheme 4**[a,b]

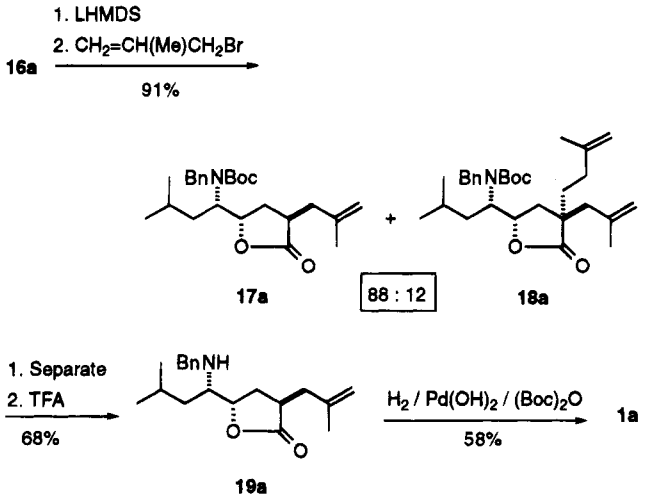



[a] Compounds **6a** and **13a**–**16a**: R = *i*-Bu; yields are quoted as the first figures under the arrows. [b]Compounds **12b**–**16b**: R = Bn; yields are quoted as the second figures under the arrows. [c]This yield refers to **15b**.

gave the same products in lower yields. Hence, crude **10a** and **10b** obtained by the nickel boride method were subjected to desilylation by treatment with tetrabutylammonium fluoride in THF at room temperature. Under these conditions, the lactonization of the resulting $\gamma$-hydroxy esters took place as well so that the isolated products were the corresponding $\gamma$-lactones **11a** ($[\alpha]_D$ −33.0 (*c* 0.9, MeOH); 31% yield from **2a**) and **11b** ($[\alpha]_D$ −5.5 (*c* 1.4, $CHCl_3$); 27% yield from **2b**). The optical rotation value of **11a** was in good agreement with that of the literature (lit.[10] $[\alpha]_D$ −33.8 (*c* 1.0, MeOH)), whereas no data were available to compare the value of **11b**. Other characteristics, such as mp's and $^1$H NMR spectra of both compounds (see the Experimental Section), were in good agreement with those of the literature. Stereoselective *anti*-alkylation at C-2 of lactones **11a** and **11b** to give the target compounds **1a** and **1b** had been reported.[10,11] Using the results of these transformations, the overall yields of **1a** and **1b** prepared by the above thiazole route were 16 and 23%, respectively.

A similar synthetic sequence was followed starting from the *N,N*-diprotected *syn* amino alcohols **6a** and **6b** (Scheme 4). These compounds were obtained in very high diastereomeric purity (ds ≥ 95%) by the reduction of the corresponding ketones **4a** and **4b** as described.[17] Pure compounds **6a** and **6b** were obtained without any problem.[21] Attempts to protect the hydroxyl group of **6a** as trialkylsilyl or benzyl ether failed under different conditions.[22] Fortunately enough, the cleavage of the thiazole ring in the presence of the free hydroxyl group[23] by the

**Scheme 5**




usual protocol[19] afforded the aldehyde **13a** in good isolated yield (78%). On the other hand, treatment of **6b** with TBDMS-triflate at room temperature gave the fully protected amino alcohol **12b** which was then converted to the aldehyde **13b** (83%). Both aldehydes **13a** and **13b** decomposed by flash chromatography with silica gel. However, crude products appeared pure as analyzed by $^1$H NMR and therefore were employed for the subsequent olefination reaction. In both cases, the reaction with the stabilized ylide ((methoxycarbonyl)methylene)-triphenylphosphorane proceeded with high selectivity to give the corresponding (*E*)-enoates **14a** and **14b** in essentially quantitative yields. Then, the reduction of the ethylenic double bond of these compounds was carried out with nickel boride.[20] Since the reaction with **14a** produced a mixture of the saturated ester **15a** and the $\gamma$-lactone **16a** in comparable amounts, the lactonization of the ester was completed by treatment with acetic acid in refluxing toluene. The compound **16a** was isolated in 85% overall yield. On the other hand the reduction of **14b** afforded the ester **15b** exclusively which upon treatment with tetrabutylammonium fluoride in THF lactonized to **16b** (86%).

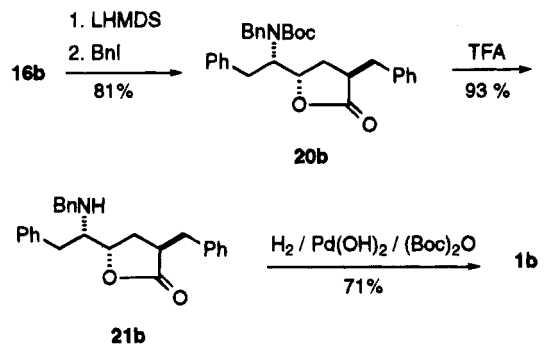
At this stage, we sought two routes which could lead to the target products **1a** and **1b** from the the lactones **16a** and **16b**. Since the removal of the *N*-benzyl group as the first step would give the $\gamma$-lactones **11a** and **11b** whose *trans* alkylation at C-2 had been already described,[10,11] we decided to follow another synthetic sequence. The alkylation of **16a** was carried out with methallyl bromide under conditions similar to those described by Kleinman[10] for **11a**, i.e., the anion generation at −78 °C with 1.2 equiv of LHMDS and then addition of 1.1 equiv of electrophile followed by slow warming at −40 °C. This reaction afforded a mixture of the *trans* monoalkylated lactone **17a** and the dialkylated product **18a** in an 88:12 ratio and 91% overall yield (Scheme 5). Chromatographic separation of the mixture gave the product **17a** in 75% yield. Attempts to suppress the formation of **18a** by the use of the less reactive metallyl chloride failed because this reagent was inert under the above conditions. The debenzylation of **17a** by catalytic hydrogenation over $Pd(OH)_2$ failed at various pressures up to 10 atm. The temporary removal of the Boc group allowed us to perform this reaction under the usual mild conditions.[24] Thus, **17a** upon treatment with a 5.2 M solution of TFA in $CH_2Cl_2$ was transformed into the *N*-benzyl 4-alkylamino lactone **19a** (90%), which

(21) The overall yield of these compounds from the corresponding amino acids **2a** and **2b** was 78% for both **6a** and **6b**.

(22) Silylation: (a) TBDMS–triflate, $Et_3N$, DMF, rt; (b) TBDMSCl, imidazole, DMF, 100 °C; (c) TBDMSCl, KH, DMF, rt; (d) $Et_3Si$–triflate, $Et_3N$, DMF, rt; (e) $Et_3SiCl$, imidazole, DMF, 100 °C. Benzylation: BnBr, NaH, DMF, rt.

(23) More frequently, the application of the thiazolyl-to-formyl deblocking protocol to compounds having unprotected hydroxyl groups leads to aldehydes in very low yield or not at all (see ref 19).

**Scheme 6**




underwent nitrogen debenzylation and reduction of the side chain by catalytic hydrogenation over $Pd(OH)_2$ at 1 atm of pressure and room temperature. Since this reaction was carried out in the presence of $(Boc)_2O$, the final product was the desired lactone **1a** (19.2% yield from **2a**) showing mp 129–130 °C and $[\alpha]_D$ −31.5 (*c* 0.8, $CH_3OH$) in excellent agreement with the literature values[10] (mp 130–131 °C, $[\alpha]_D$ −32.0 (*c* 1.0, MeOH)).

The alkylation of **16b** was accomplished by reaction with benzyl iodide (Scheme 6), while benzyl bromide appeared unreactive under the same reaction conditions. The anion generation with 1.2 equiv of LHMDS and then quenching with the electrophile produced exclusively the *trans* benzylated lactone **20b** although in low yield (50%). The yield was increased to 81% by the use of 2.0 equiv of LHMDS. Also in this case, the removal of the *N*-benzyl group failed in the presence of the Boc group. Hence, **20b** was converted to the *N*-benzyl derivative **21b** whose catalytic hydrogenation in the presence of $(Boc)_2O$ afforded **1b** (23.3% yield from **2b**) showing mp 78–80 °C and $[\alpha]_D$ −16.5 (*c* 1.2, $CHCl_3$) in good agreement with the literature values (lit.[11] mp 76–78 °C; lit.[12] mp 89–91 °C; $[\alpha]_D$ −17.3 (*c* 1.2, $CHCl_3$)).

In conclusion, the lactones **1a** and **1b** have been prepared from the corresponding α-amino acids L-leucine (**2a**) and L-phenylalanine (**2b**) through thiazole-based routes in overall yields (19–23%) comparable with those of earlier literature methods. Although the synthetic route employing β-amino alcohols with doubly protected nitrogen requires more steps[25] than the route employing singly protected compounds, the former approach gives good results owing to very high diastereoselectivities and yields of key steps. These synthetic routes should be viable for the synthesis of various hydroxyethylene dipeptide isosteres with structural diversity at C-2 and C-5.

## Experimental Section

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[26] and freshly distilled prior to use. Flash column chromatography[27] was performed on silica gel 60 (230–400 mesh). Reactions were monitored by TLC on silica gel 60 $F_{254}$ with detection by charring with ninhydrin or sulfuric acid alcoholic solutions. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C in the stated solvent. $^1H$ (300 MHz) and $^{13}C$ (75 MHz) NMR were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified.

**(1′*R*,2′*S*)-2-[2′-[*N*-(*tert*-Butoxycarbonyl)amino]-1′-[(*tert*-butyldimethylsilyl)oxy]-4′-methylpentyl]-1,3-thiazole (7a).** To a stirred solution of the crude amino alcohol **5a**[16b] (0.80 g, 2.66 mmol) in dry DMF (6 mL) were added imidazole (0.36 g, 5.32 mmol), DMAP (catalytic), and *tert*-butyldimethylsilyl chloride (0.30 g, 1.99 mmol). After being stirred for 18 h at rt, the solution was diluted with MeOH (3 mL), stirred at the same temperature for an additional 1 h, and then concentrated. The residue was treated with $H_2O$ (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated to give a crude syrup. Flash chromatography on silica gel (4:1 $CH_2Cl_2$–EtOAc) gave pure **7a** (0.90 g, 82%) as a syrup: $[\alpha]_D$ −80.6 (*c* 0.9, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 120 °C) δ 0.01 (s, 3 H), 0.15 (s, 3 H), 0.85 (d, 3 H, *J* = 2.5 Hz), 0.87 (d, 3 H, *J* = 2.5 Hz), 0.92 (s, 9 H), 1.10–1.30 (m, 2 H), 1.39 (s, 9 H), 1.56–1.70 (m, 1 H), 3.83 (ddd, 1 H, *J* = 4.8, 9.1, 14.9 Hz), 5.01 (d, 1 H, *J* = 4.8 Hz), 5.76–5.86 (m, 1 H), 7.58 (d, 1 H, *J* = 3.1 Hz), 7.75 (d, 1 H, *J* = 3.1 Hz). Anal. Calcd for $C_{20}H_{38}N_2O_3SSi$: C, 57.92; H, 9.24; N, 6.75. Found: C, 57.66; H, 8.94; N, 7.03.

Second eluted (0.12 g, 10.8%) was the 1′*S* epimer of **7a**: white solid; mp 73–75 °C; $[\alpha]_D$ −44.8 (*c* 0.5, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 120 °C) δ −0.03 (s, 3 H), 0.06 (s, 3 H), 0.76 (d, 3 H, *J* = 6.9 Hz), 0.83 (d, 3 H, *J* = 6.9 Hz), 0.95 (s, 9 H), 1.08–1.48 (m, 2 H), 1.37 (s, 9 H), 1.50–1.69 (m, 1 H), 3.80–3.94 (m, 1 H), 5.02 (d, 1 H, *J* = 5.0 Hz), 5.85–6.11 (m, 1 H), 7.57 (d, 1 H, *J* = 3.0 Hz), 7.72 (d, 1 H, *J* = 3.0 Hz). Anal. Calcd for $C_{20}H_{38}N_2O_3SSi$: C, 57.92; H, 9.24; N, 6.75. Found: C, 57.86; H, 9.56; N, 6.83.

**(1′*R*,2′*S*)-2-[2′-[*N*-(*tert*-Butoxycarbonyl)amino]-1′-[(*tert*-butyldimethylsilyl)oxy]-3′phenylpropyl]-1,3-thiazole (7b).** The mixture of the *syn* amino alcohol **5b** and its anti isomer[16b] (0.90 g, 2.69 mmol) was treated as described above to give **7b** and its 1′*S* epimer[16b] in 78:22 ratio. These products were separated by flash chromatography on silica gel (4:1 $CH_2Cl_2$–EtOAc). Pure **7b**: (0.92 g, 76%); $[\alpha]_D$ −6.3 (*c* 1.1, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 120 °C) δ 0.01 (s, 3 H), 0.15 (s, 3 H), 0.94 (s, 9 H), 1.25 (s, 9 H), 2.51 (dd, 1 H, *J* = 10.8, 14.1 Hz), 2.82 (dd, 1 H, *J* = 3.8, 14.1 Hz), 3.95–4.06 (m, 1 H), 5.12 (d, 1 H, *J* = 4.5 Hz), 5.83–6.01 (m, 1 H), 7.10–7.22 (m, 5 H), 7.60 (d, 1 H, *J* = 3.1 Hz), 7.76 (d, 1 H, *J* = 3.1 Hz). Anal. Calcd for $C_{23}H_{36}N_2O_3SSi$: C, 61.57; H, 8.09; N, 6.24. Found: C, 61.90; H, 8.41; N, 5.90.

**(2*R*,3*S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-5-methylhexanal (8a).** A mixture of the thiazole derivative **7a** (0.80 g, 1.92 mmol) and actived 4 Å powdered molecular sieves (1.80 g) in $CH_3CN$ (20 mL) was stirred at rt for 10 min and then treated with methyl triflate (0.28 mL, 2.50 mmol). The suspension was stirred for 30 min and then concentrated to dryness (bath temperature below 40 °C). The residue was suspended in $CH_3OH$ (20 mL), cooled (ice bath), and treated with $NaBH_4$ (0.16 g, 4.22 mmol). The resulting mixture was stirred at rt for an additional 10 min, diluted with acetone (1 mL), filtered through Celite, and concentrated. To a solution of the residue in 10:1 $CH_3CN/H_2O$ (20 mL) were added CuO (1.52 g, 19.2 mmol) and, portionwise under vigorous stirring, $CuCl_2 \cdot 2H_2O$ (0.32 g, 1.92 mmol). The dark mixture was stirred for 15 min and then filtered through Celite and concentrated (bath temperature below 40 °C). The brown syrup residue was triturated with $Et_2O$ (5 × 20 mL), and the liquid phase was pipetted and filtered through a pad of Florisil (100–200 mesh). The ethereal solution was concentrated (bath temperature below 40 °C) to give the crude aldehyde **8a** (0.52 g, 75%; 95% pure by $^1H$ NMR) as a clear yellow syrup: $^1H$ NMR (DMSO-$d_6$, 120 °C) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.90 (d, 6 H, *J* = 6.4 Hz), 0.92 (s, 9 H), 1.27–1.42 (m, 2 H), 1.40 (s, 9 H), 1.57–1.72 (m, 1 H), 3.89 (ddd, 1 H, *J* = 3.8, 8.9, 14.1 Hz), 4.01 (dd, 1 H, *J* = 1.3, 3.8 Hz), 5.87–6.0 (m, 1

(24) *N*-Debenzylation in the presence of the Boc group has been described by the use of $Na/NH_3$ (Jurczak, J.; Golebiowski, A. *Synlett* **1993**, 241). However, these conditions were scarcely compatible with the stability of the lactone ring of **17a**.

(25) It is expected that this route can be improved by the use of the *p*-methoxybenzyl (PMB) and Boc for the amino group diprotection (see ref 16b). Suitable changes of the reaction sequence should be possible owing to the PMB group removal under oxidative conditions.

(26) Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*; Pergamon: New York, 1988.

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

H), 9.57 (d, 1 H, $J$ = 1.3 Hz). Attempts to purify this compound by flash chromatography led to extensive decomposition.

**(2*R*,3*S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenylbutanal (8b).** The same procedure as described above for **7a** was applied to **7b** (0.85 g, 1.89 mmol) to give the crude aldehyde **8b** (0.59 g, 79%; 95% pure by $^1$H NMR) as a clear yellow syrup: $^1$H NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.96 (s, 9 H), 1.30 (s, 9 H), 2.73 (dd, 1 H, $J$ = 9.9, 14.5 Hz), 2.88 (dd, 1 H, $J$ = 4.6, 14.5 Hz), 4.04–4.15 (m, 1 H), 4.21 (dd, 1 H, $J$ = 1.0, 5.2 Hz), 6.0–6.14 (m, 1 H), 7.12–7.31 (m, 5 H), 9.59 (d, 1 H, $J$ = 1.0 Hz). Attempts to purify this compound by flash chromatography led to extensive decomposition.

**Methyl (4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-[(*tert*-butyldimethylsilyl)oxy]-7-methyl-2(*E*,*Z*)-octenoate (9a).** To a stirred solution of the crude aldehyde **8a** (0.51 g, 1.42 mmol) in dry toluene (10 mL) was added ((methoxycarbonyl)methylene)triphenylphosphorane (0.84 g, 2.4 mmol). The solution was stirred for 18 h at rt and then concentrated. Flash chromatography on silica gel of the residue (7:3 hexane–$Et_2O$) afforded **9a** (0.48 g, 82%) as a mixture of *E*- and *Z*-isomers in a 65:35 ratio: $^1$H NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.02 (s, 1.05 H), 0.06 (s, 1.05 H), 0.08 (s, 1.95 H), 0.12 (s, 1.95 H), 0.82–0.90 (m, 6 H), 0.90 (s, 3.15 H), 0.93 (s, 5.85 H), 1.22–1.36 (m, 2 H), 1.39 (s, 3.15 H), 1.41 (s, 5.85 H), 3.56–3.66 (m, 1 H), 3.69 (s, 3H), 4.55–4.42 (m, 0.65 H), 5.21 (dd, 0.35 H, $J$ = 5.6, 7.7 Hz), 5.50–5.60 (m, 0.35 H), 5.62–5.66 (m, 0.65 H), 5.83 (dd, 0.35 H, $J$ = 1.8, 11.0 Hz), 5.95 (dd, 0.65 H, $J$ = 1.9, 15.4 Hz), 6.10 (dd, 0.35 H, $J$ = 7.7, 11.0 Hz), 6.91 (dd, 0.65 H, $J$ = 4.4, 15.4 Hz). Anal. Calcd for $C_{21}H_{41}NO_5Si$: C, 60.71; H, 9.92; N, 3.37. Found: C, 61.03; H, 9.67; N, 3.65.

**Methyl (4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-2(*E*,*Z*)-hexenoate (9b).** The reaction was carried out as described above starting from crude **9b** (0.55 g, 1.39 mmol). Flash chromatography on silica gel (94:6 $CH_2Cl_2$–$Et_2O$) gave **9b** (0.50 g, 80%) as a mixture of *E*- and *Z*-isomers in a 75:25 ratio: $^1$H NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.04 (s, 0.75 H), 0.10 (s, 2.25 H), 0.11 (s, 0.75 H), 0.16 (s, 2.25 H), 0.92 (s, 2.25 H), 0.97 (s, 6.75 H), 1.26 (s, 2.25 H), 1.30 (s, 6.75 H), 2.51 (dd, 0.75 H, $J$ = 10.7, 14.6 Hz), 2.66 (dd, 0.25 H, $J$ = 9.9, 14.0 Hz), 2.84 (dd, 0.75 H, $J$ = 3.3, 14.6 Hz), 2.86 (dd, 0.25 H, $J$ = 4.9, 14.0 Hz), 3.65 (s, 0.75 H), 3.70 (s, 2.25 H), 3.76–3.88 (m, 1 H), 4.49 (ddd, 0.75 H, $J$ = 1.6, 4.9, 6.6 Hz), 5.31 (ddd, 0.25 H, $J$ = 1.3, 5.8, 9.1 Hz), 5.73–5.82 (m, 0.25 H), 5.88 (dd, 0.25 H, $J$ = 1.3, 11.5 Hz), 6.02 (dd, 0.75 H, $J$ = 1.6, 14.8 Hz), 6.17 (dd, 0.25 H, $J$ = 9.1, 11.5 Hz), 6.21–6.32 (m, 0.75 H), 6.98 (dd, 0.75 H, $J$ = 4.9, 14.8 Hz), 7.12–7.28 (m, 5 H). Anal. Calcd for $C_{24}H_{39}NO_5Si$: C, 64.11; H, 8.74; N, 3.11. Found: C, 64.45; H, 9.04; N, 3.43.

**Methyl (4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-[(*tert*-butyldimethylsilyl)oxy]-7-methyloctanoate (10a).** To a cold (ice bath) solution of **9a** (0.48 g, 1.15 mmol) in dry $CH_3OH$ (12 mL) were added 11.5 mL of a 4% $CH_3OH$ solution of $NiCl_2 \cdot 6H_2O$ (1.96 mmol). The solution was stirred for 30 min at 0 °C and then treated portionwise with $NaBH_4$ (0.17 g, 4.60 mmol). The resulting black mixture was stirred for an additional 1 h at 0 °C, and then the ice bath was removed. After 18 h at rt the mixture was treated with AcOH (2–3 drops), filtered through Celite, and concentrated. The residue was partitioned between saturated $NaHCO_3$ solution (15 mL) and $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated to give crude **10a** (0.46 g, 97%; 95% pure by $^1$H NMR) as a syrup which was utilized for the next reaction without purification. An analytical sample of **10a** was obtained by chromatography on silica gel (7:3 hexane–$Et_2O$): $[\alpha]_D$ −16.7 (*c* 0.4, $CHCl_3$); $^1$H NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.08 (s, 3 H), 0.11 (s, 3 H), 0.86–0.93 (m, 6 H), 0.90 (s, 9 H), 1.27–1.38 (m, 2 H), 1.41 (s, 9 H), 1.52–1.70 (m, 2 H), 1.74–1.87 (m, 1 H), 2.31–2.38 (m, 1 H), 3.52–3.60 (m, 1 H), 3.61 (s, 3 H), 3.62–3.71 (m, 1 H), 5.68–5.78 (m, 1 H). Anal. Calcd for $C_{21}H_{43}NO_5Si$: C, 60.41; H, 10.38; N, 3.35. Found: C, 60.14; H, 10.10; N, 3.05.

**Methyl (4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-[(*tert*-butyldimethylsilyl)oxy]-6-phenylhexanoate (10b).** A cold (ice bath) solution of **9b** (0.40 g, 0.89 mmol) in $CH_3OH$ (9 mL) was treated as described above to give crude **10b** (0.37 g, 93%; 95% pure by $^1$H NMR) which was used for the next reaction without purification. An analytical sample of **10b** was obtained after flash chromatography on silica gel (7:3 hexane–$Et_2O$): $[\alpha]_D$ −10.8 (*c* 0.8, $CHCl_3$); $^1$H NMR (DMSO-$d_6$, 120 °C), $\delta$ 0.10 (s, 3 H), 0.15 (s, 3 H), 0.94 (s, 9 H), 1.30 (s, 9 H), 1.60–1.75 (m, 1 H), 1.83–1.97 (m, 1 H), 2.33–2.41 (m, 2 H), 2.62 (dd, 1 H, $J$ = 10.9, 14.9 Hz), 2.85 (dd, 1 H, $J$ = 3.3, 14.9 Hz), 3.60 (s, 3 H), 3.71–3.82 (m, 2 H), 5.88–6.20 (m, 1 H), 7.12–7.30 (m, 5 H). Anal. Calcd for $C_{24}H_{41}NO_5Si$: C, 63.82; H, 9.15; N, 3.10. Found: C, 63.59; H, 9.00; N, 2.91.

**(5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butoxycarbonyl)amino]-3′-methylbutyl]dihydrofuran-2(3*H*)-one (11a).** A solution of **10a** (0.40 g, 0.96 mmol) in THF (10 mL) was treated at rt with $Bu_4NF \cdot 3H_2O$ (0.46 g, 1.43 mmol). After 2 h, the solution was diluted with $H_2O$ (20 mL) and EtOAc (10 mL). The two phases were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated. Flash chromatography on silica gel of the residue (1:1 hexane–$Et_2O$) afforded pure **11a** (0.23 g, 87%) as a white solid: mp 73–75 °C; $[\alpha]_D$ −33.0 (*c* 0.9, $CH_3OH$); (lit.[10] mp 76–77 °C; $[\alpha]_D$ −33.8 (*c* 1.0, $CH_3OH$)); $^1$H NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.88 (d, 3 H, $J$ = 6.8 Hz), 0.92 (d, 3 H, $J$ = 6.8 Hz), 1.16–1.52 (m, 2 H), 1.41 (s, 9 H), 1.58–1.73 (m, 1 H), 1.86–2.02 (m, 1 H), 2.10–2.22 (m, 1 H), 2.32–2.52 (m, 2 H), 3.58–3.72 (m, 1 H), 4.38–4.47 (m, 1 H), 6.20–6.32 (m, 1 H); $^{13}$C NMR $\delta$ 21.8, 23.0, 23.1, 24.1, 24.7, 28.2, 42.1, 50.9, 79.7, 82.5, 156.0, 177.4. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 10.77; N, 5.16. Found: C, 62.00; H, 10.06; N, 4.86.

**(5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butoxycarbonyl)amino]-2′-phenylethyl]dihydrofuran-2(3*H*)-one (11b).** The reaction was carried out as described above for **11a** starting from **10b** (0.35 g, 0.77 mmol) to give after flash chromatography (1:1 hexane–$Et_2O$) 0.19 g of pure **11b** (81%) as a white solid: mp 93–95 °C (lit.[11] mp 95 °C); $[\alpha]_D$ −5.5 (*c* 1.4, $CHCl_3$); $^1$H NMR $\delta$ 1.40 (s, 9 H), 2.07–2.19 (m, 2 H), 2.42–2.60 (m, 2 H), 2.88 (dd, 1 H, $J$ = 7.5, 13.5 Hz), 2.96 (dd, 1 H, $J$ = 7.0, 13.5 Hz), 3.97–4.08 (m, 1 H), 4.48 (dddd, 1 H, $J$ = 1.5, 7.0, 7.5, 10.0 Hz), 4.64 (d, 1 H, $J$ = 10.0 Hz), 7.20–7.35 (m, 5 H); $^{13}$C NMR $\delta$ 24.1, 28.2, 28.7, 39.4, 54.0, 79.9, 80.0, 126.4, 126.7, 128.6, 129.3, 137.1, 155.8, 177.2. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 4.58; N, 7.60. Found: C, 65.13; H, 4.26; N, 7.33.

**(1′*R*,2′*S*)-2-[2′-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-1′-[(*tert*-butyldimethylsilyl)oxy]-3′-phenylpropyl]-1,3-thiazole (12b).** To a stirred solution of crude **6b**[17] (0.80 g, 1.88 mmol) in dry DMF (4 mL) were added $Et_3N$ (0.38 mL, 2.8 mmol), DMAP (catalytic), and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.52 mL, 2.26 mmol). After being stirred for 1 h at rt, the solution was concentrated, and the residue was treated with $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated to give a crude syrup. Chromatography on silica gel (7:3 hexane–$Et_2O$) gave pure **12b** (0.92 g, 90%) as a syrup: $[\alpha]_D$ −7.7 (*c* 1.5, $CHCl_3$); $^1$H NMR (DMSO-$d_6$, 120 °C) $\delta$ −0.15 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 1.34 (s, 9 H), 2.56–2.68 (m, 1 H), 2.90–3.08 (m, 1 H), 4.34–4.43 (m, 1 H), 4.46 (d, 1 H, $J$ = 15.3 Hz), 4.50 (d, 1 H, $J$ = 15.3 Hz), 5.46 (d, 1 H, $J$ = 6.7 Hz), 6.74–6.84 (m, 2 H), 6.96–7.10 (m, 5 H), 7.10–7.19 (m, 3 H), 7.63 (d, 1 H, $J$ = 3.1 Hz), 7.25 (d, 1 H, $J$ = 3.1 Hz). Anal. Calcd for $C_{30}H_{42}N_2O_3SSi$: C, 66.88; H, 7.86; N, 5.20. Found: C, 66.72; H, 8.16; N, 5.46.

**(2*R*,3*S*)-3-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-2-hydroxy-5-methylhexanal (13a).** A mixture of the thiazole derivative **6a**[17] (0.8 g, 2.0 mmol), activated 4 Å powdered molecular sieves (4.0 g), and anhydrous $CH_3CN$ (20 mL) was stirred a rt for 10 min, and then methyl triflate (0.30 mL, 2.60 mmol) was added. The suspension was stirred for 15 min and then concentrated to dryness. The residue was suspended in $CH_3OH$ (20 mL), cooled (0 °C), and treated with $NaBH_4$ (0.17 g, 4.40 mmol). The mixture was stirred at rt for 10 min, diluted with acetone (1–2 drops), filtered through Celite, and concentrated. The solution of the residue in 10:1 $CH_3CN$–$H_2O$ (19 mL) was treated with a solution of $HgCl_2$ (0.53 g, 2.0 mmol) in the same solvent mixture (1 mL). The mixture was stirred for 15 min at rt and then filtered through Celite and concentrated (bath temperature not exceeding 40 °C). The residue was dissolved in $CH_2Cl_2$ (15 mL) and washed with 20%

aqueous KI (15 mL), and the two phases were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 15 mL), and the combined organic layers were dried ($Na_2SO_4$) and concentrated. The residue was dissolved in $Et_2O$ and quickly filtered through a pad of Florisil to give crude **13a** (0.52 g, 78%; 95% pure by $^1H$ NMR) as a clear yellow solid: mp 57–59 °C; $^1H$ NMR (selected data) $\delta$ 0.77 (d, 3 H $J$ = 6.8 Hz), 0.87 (d, 3 H, $J$ = 6.8 Hz), 1.39 (s, 9 H), 7.15–7.40 (m, 5 H), 9.70 (s, 1 H). Attempts to purify this compound by flash chromatography led to extensive decomposition.

**(2*R*,3*S*)-3-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenylbutanal (13b).** The same procedure as described above for **13a** was applied to **12b** (0.85 g, 1.58 mmol) to give the crude aldehyde **13b** (0.67 g, 83%; 95% pure by $^1H$ NMR) as a clear yellow syrup: $^1H$ NMR (DMSO-$d_6$, 100 °C) $\delta$ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.92 (s, 9 H) 1.27 (s, 9 H), 2.93 (dd, 1 H, $J$ = 5.9, 14.7 Hz), 3.07 (dd, 1 H, $J$ = 9.5, 14.7 Hz), 4.32 (d, 1 H, $J$ = 16.1 Hz), 4.42 (d, 1 H, $J$ = 16.1 Hz), 4.45 (dd, 1 H, $J$ = 1.2, 6.1 Hz), 4.70 (ddd, 1 H, $J$ = 5.9, 6.1, 9.5 Hz), 7.01–7.29 (m, 10 H), 9.80 (d, 1 H, $J$ = 1.2 Hz). Attempts to purify this compound by flash chromatography led to extensive decomposition.

**Methyl (4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-4-hydroxy-7-methyl-2(*E*)-octenoate (14a).** To a stirred solution of the crude aldehyde **13a** (0.50 g, 1.49 mmol) in dry toluene (15 mL) was added ((methoxycarbonyl)methylene)-triphenylphosphorane (0.55 g, 1.64 mmol). The solution was stirred for 24 h at rt and then concentrated. Flash chromatography on silica gel (7:3 hexane–$Et_2O$) afforded pure **14a** (0.55 g, 95%) as a syrup: $[\alpha]_D$ −16.2 (*c* 0.6, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.71 (d, 3 H, $J$ = 6.6 Hz), 0.81 (d, 3 H, $J$ = 6.4 Hz), 1.23–1.60 (m, 3 H), 1.36 (s, 9 H), 3.68 (s, 3 H), 4.08 (ddd, 1 H, $J$ = 5.2, 8.6, 9.9 Hz) 4.32 (ddd, 1 H, $J$ = 1.6, 4.9, 5.2 Hz), 4.42 (s, 2 H), 5.0 (bs, 1 H, ex $D_2O$), 6.03 (dd, 1 H $J$ = 1.6, 15.6 Hz), 6.91 (dd, 1 H, $J$ = 4.9, 15.6 Hz), 7.12–7.22 (m, 5 H). Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.57. Found: C, 67.73; H, 8.64; N, 3.74.

**Methyl (4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-4-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-2(*E*)-hexenoate (14b).** The Wittig reaction was carried out as described above for **14a** starting from the crude aldehyde **13b** (0.65 g, 1.26 mmol). Flash chromatography (silica gel, 4:1 hexane–$Et_2O$) gave pure **14b** (0.67 g, 98%) as a syrup: $[\alpha]_D$ −34.9 (*c* 1.9, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 130 °C) $\delta$ 0.03 (s, 3 H), 0.09 (s, 3 H), 0.92 (s, 9 H) 1.29 (s, 9 H), 2.85 (dd, 1 H, $J$ = 7.3, 14.6 Hz), 2.99 (dd, 1 H, $J$ = 9.2, 14.6 Hz), 3.68 (s, 3 H), 4.35 (ddd, 1 H, $J$ = 5.4, 7.3, 9.2 Hz), 4.36 (d, 1 H, $J$ = 16.4 Hz), 4.46 (d, 1 H, $J$ = 16.4 Hz), 4.69 (ddd, 1 H, $J$ = 1.3, 5.4, 6.1 Hz), 5.99 (dd, 1 H, $J$ = 1.3, 15.9 Hz), 6.86 (dd, 1 H, $J$ = 6.1, 15.9 Hz), 6.98–7.21 (m, 10 H). Anal. Calcd for $C_{31}H_{45}NO_5Si$: C, 68.98; H, 8.40; N, 2.59. Found: C, 69.24; H, 8.63; N, 2.72.

**Methyl (4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-4-[(*tert*-butyldimethylsilyl)oxy]-6-phenylhexanoate (15b).** A cold (ice bath) solution of **14b** (0.65 g, 1.2 mmol) in dry $CH_3OH$ (12 mL) was reduced as described above for **9a** to give crude **15b** (0.58 g, 89%; 95% pure by $^1H$ NMR) as a syrup. An analytical sample of **15b** was obtained by chromatography on silica gel (4:1 hexane–$Et_2O$): $[\alpha]_D$ −273.8 (*c* 0.5, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 140 °C) $\delta$ 0.09 (s, 3 H), 0.12 (s, 3 H), 0.92 (s, 9 H), 1.29 (s, 9 H), 1.76–2.10 (m, 2 H), 2.28–2.48 (m, 2 H), 2.86 (dd, 1 H, $J$ = 4.9, 14.7 Hz), 3.21 (dd, 1 H, $J$ = 9.8, 14.7 Hz), 3.60 (s, 3 H), 3.99–4.07 (m, 1 H), 4.32–4.41 (m, 1 H), 4.45 (d, 2 H, $J$ = 16.0 Hz), 7.01–7.26 (m, 10 H). Anal. Calcd for $C_{31}H_{47}NO_5Si$: C, 68.72; H, 8.74; N, 2.58. Found: C, 68.93; H, 8.39; N, 2.93.

**(5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-3′-methylbutyl]dihydrofuran-2(3*H*)-one (16a).** A cold (0 °C) stirred solution of **14a** (0.50 g, 1.28 mmol) in dry $CH_3OH$ (13 mL) was processed as described above for **9a**. After the usual workup, the $^1H$ NMR of the crude residue (0.45 g) showed the presence of a mixture of **15a** and **16a**. A solution of this mixture in toluene (12 mL) and AcOH (0.3 mL) was refluxed for 3 h and then concentrated. Flash chromatography on silica gel of this material (20:1 $CH_2Cl_2$–EtOAc) afforded pure **16a** (0.39 g, 85%) as a syrup: $[\alpha]_D$ −2.1 (*c* 1.3, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.72 (d, 3 H, $J$ = 6.7 Hz), 0.82 (d, 3 H, $J$ = 6.5 Hz), 1.12 (ddd, 1 H, $J$ = 3.9, 9.2, 14.4 Hz), 1.38 (s, 9 H), 1.40 −1.51 (m, 1 H), 1.58 (ddd, 1 H, $J$ = 3.9, 10.5, 14.4 Hz), 1.86 (dddd, 1 H, $J$ = 7.8, 9.1, 12.4, 16.4 Hz), 2.24 (dddd, 1 H, $J$ = 4.6, 6.5, 9.1, 16.4 Hz), 2.35–2.58 (m, 2 H), 4.08 (ddd, 1 H, $J$ = 3.6, 7.9, 10.6 Hz), 4.33 (d, 1 H, $J$ = 15.6 Hz), 4.41 (d, 1 H, $J$ = 15.6 Hz), 4.53–4.62 (m, 1 H), 7.18–7.35 (m, 5 H). Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.64; N, 3.87. Found: C, 69.91; H, 8.81; N, 4.06.

**(5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-2′-phenylethyl]dihydrofuran-2(3*H*)-one (16b).** A solution of crude **15b** (0.50 g, 0.92 mmol) in THF (9 mL) was treated at rt with $Bu_4NF{\cdot}3H_2O$ (0.32 g, 1.01 mmol). After 4 h, the solution was diluted with $H_2O$ (20 mL) and EtOAc (10 mL). The two phases were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated. Flash chromatography on silica gel of the residue (3:2 hexane–$Et_2O$) afforded pure **16b** (0.31 g, 86%) as a white solid: mp 81–82 °C; $[\alpha]_D$ −16.9 (*c*, 1.1, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 140 °C) $\delta$ 1.35 (s, 9 H), 1.91 (dddd, 1 H, $J$ = 7.5, 9.5, 13.2, 18.3 Hz), 2.21 (dddd, 1 H, $J$ = 4.4, 6.8, 9.5, 18.3 Hz), 2.37 (ddd, 1 H, $J$ = 4.4, 9.5, 17.0 Hz), 2.43–2.56 (m, 1 H), 2.87 (dd, 1 H, $J$ = 5.2, 13.6 Hz), 2.99 (dd, 1 H, $J$ = 8.8, 13.6 Hz), 4.16–4.26 (m, 1 H), 4.26 (d, 1 H, $J$ = 15.0 Hz), 4.30 (d, 1 H $J$ = 15.0 Hz), 4.69–4.79 (m, 1 H), 7.09–7.27 (m, 10 H). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.88; H, 7.39; N, 3.54. Found: C, 73.01; H, 7.18; N, 3.87.

**(3*R*,5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-3′-methylbutyl]-3-(2-methylprop-2-enyl)dihydrofuran-2(3*H*)-one (17a) and (5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-3′-methylbutyl]-3,3-bis(2-methylprop-2-enyl)dihydrofuran-2(3*H*)-one (18a).** To a cold (0 °C) stirred solution of hexamethyldisilazane (0.25 mL, 1.21 mmol) in THF (6 mL) was added dropwise *n*-BuLi (0.73 mL, 1.16 mmol, of a 1.6 M solution in hexane). The suspension was stirred for an additional 10 min at this temperature and then cooled to −78 °C. A solution of the lactone **16a** (0.35 g, 0.97 mmol) in THF (3 mL) was added dropwise, and the resultant clear solution was stirred at this temperature for 15 min. A solution of freshly distilled methallyl bromide (0.14 g, 1.07 mmol) in THF (1 mL) was added over 3 min, and the mixture was allowed to warm to −40 °C over 1.5 h and then treated with aqueous phosphate buffer (pH 7, 15 mL) and allowed to warm to rt. The mixture was treated with EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried ($Na_2SO_4$) and concentrated. The crude residue (0.37 g, 91%; 95% pure by $^1H$ NMR) was a mixture of **17a** and **18a** in 88:12 ratio. Flash chromatography on silica gel (3:2 hexane–$Et_2O$) afforded first pure **18a** (43.0 mg, 9.4%) and then pure **17a** (0.30 g, 75%) as syrups.

**17a**: $[\alpha]_D$ −10.0 (*c* 0.9, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.72 (d, 3 H, $J$ = 6.6 Hz), 0.83 (d, 3 H, $J$ = 6.6 Hz), 1.11 (ddd, 1 H, $J$ = 3.4, 9.1, 13.7 Hz), 1.36 (s, 9 H), 1.40–1.61 (m, 2 H), 1.70 (s, 3 H), 1.87–2.12 (m, 2 H), 2.16 (dd, 1 H, $J$ = 9.9, 14.8 Hz), 2.40 (dd, 1 H, $J$ = 4.9, 14.8 Hz), 2.68–2.81 (m, 1 H), 4.08 (ddd, 1 H, $J$ = 3.4, 8.5, 10.7 Hz), 4.31 (d, 1 H, $J$ = 16.4 Hz), 4.42 (d, 1 H, $J$ = 16.4 Hz), 4.56 (ddd, 1 H, $J$ = 5.6, 7.3, 8.5 Hz), 4.75 (s, 1 H), 4.81 (s, 1 H), 7.15–7.35 (m, 5 H). Anal. Calcd for $C_{27}H_{37}NO_4$: C, 72.27; H, 8.98; N, 3.37. Found: C, 72.53; H, 9.27; N, 3.61.

**18a**: $[\alpha]_D$ +92.3 (*c* 1.5, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 120 °C) $\delta$ 0.72 (d, 3 H, $J$ = 6.7 Hz), 0.81 (d, 3 H, $J$ = 6.7 Hz), 1.02–1.30 (m, 1 H), 1.40 (s, 9 H), 1.41–1.61 (m, 1 H), 1.69 (s, 3 H), 1.71 (s, 3 H), 1.93 (dd, 1 H, $J$ = 9.4, 13.5 Hz), 2.17 (dd, 1 H, $J$ = 6.7, 13.5 Hz), 2.21–2.45 (m, 5 H), 3.93–4.05 (m, 1 H), 4.37 (s, 2 H), 4.38–4.47 (m, 1 H), 4.75 (bs, 1 H), 4.80 (bs, 1 H), 4.86 (bs, 1 H), 4.92 (bs, 1 H), 7.19–7.32 (m, 5 H). Anal. Calcd for $C_{29}H_{43}NO_4$: C, 74.17; H, 9.23; N, 2.98. Found: C, 73.82; H, 9.03; N, 3.10.

**(3*R*,5*S*,1′*S*)-5-[1′-(*N*-Benzylamino)-3′-methylbutyl]-3-(2-methylprop-2-enyl)dihydrofuran-2(3*H*)-one (19a).** The lactone **18a** (0.30 g, 0.72 mmol), was tretated with a 5.2 M solution of TFA in $CH_2Cl_2$ (10 mL) at rt. After 10 min of vigorous stirring the solution was cooled (0 °C) and carefully neutralized with saturated $NaHCO_3$ solution. The phases

were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were washed with aqueous phosphate buffer (pH 7, 15 mL) and then dried ($Na_2SO_4$) and concentrated. The crude product (0.20 g, 90%; 95% pure by $^1H$ NMR) was immediately used for the next reaction without further purification: $^1H$ NMR $\delta$ 0.89 (d, 3 H, $J$ = 6.3 Hz), 0.93 (d, 3 H, $J$ = 6.3 Hz), 1.22–1.48 (m, 2 H), 1.56–1.80 (m, 1 H), 1.74 (s, 3 H), 1.84–1.96 (m, 1 H), 2.02–2.14 (m, 2 H), 2.48–2.64 (m, 2 H), 2.93–3.07 (m, 2 H), 3.73 (d, 1 H, $J$ = 12.5 Hz), 3.91 (d, 1 H, $J$ = 12.5 Hz), 4.44–4.53 (m, 1 H), 4.71 (s, 1 H), 4.81 (s, 1 H), 7.18–7.38 (m, 5 H); $^{13}C$ NMR $\delta$ 21.6, 22.4, 22.7, 24.6, 30.3, 38.0, 39.4, 40.1, 51.9, 57.9, 80.1, 96.2, 112.8, 127.4, 128.6, 128.7, 140.9, 142.8, 180.6.

**(3*R*,5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butoxycarbonyl)amino]-3′-methylbutyl]-3-(2-methylpropyl)dihydrofuran-2(3*H*)-one (1a).** To a solution of freshly prepared lactone **19a** (0.20 g, 0.63 mmol) in $CH_3OH$ (3 mL) were added $Pd(OH)_2$ (0.05 g) and $(Boc)_2O$ (0.27 g, 1.26 mmol). The suspension was hydrogenated at 1 atm for 18 h and then filtered through Celite and concentrated. Flash chromatography on silica gel of the residue (1:4 hexane–$Et_2O$) afforded pure **1a** (0.12 g, 58%) as a white solid: mp 129–130 °C; $[\alpha]_D$ −31.5 (*c* 0.8, $CH_3OH$) (lit.[10] mp 130–131 °C; $[\alpha]_D$ −32.1 (*c* 1.0, $CH_3OH$)); $^1H$ NMR $\delta$ 0.85–0.98 (m, 12 H), 1.25–1.72 (m, 6 H), 1.42 (s, 9 H), 1.89–2.10 (m, 1 H), 2.32–2.43 (m, 1 H), 2.59–2.69 (m, 1 H), 3.78–3.91 (m, 1 H), 4.35 (d, 1H, $J$ = 8.1 Hz), 4.45–4.53 (m, 1 H); $^{13}C$ NMR $\delta$ 21.2, 21.4, 21.7, 22.9, 24.6, 25.9, 28.2, 30.9, 37.6, 40.5, 41.8, 51.8, 79.8, 80.4, 156.2, 180.5. Anal. Calcd for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16; N, 4.28. Found: C, 66.30; H, 9.96; N, 4.10.

**(3*R*,5*S*,1′*S*)-3-Benzyl-5-[1′-[*N*-(*tert*-Butoxycarbonyl)benzylamino]-2′-phenylethyl]dihydrofuran-2(3*H*)-one (20b).** To a cold (−78 °C) solution of lithium hexamethyldisilazide (1.52 mmol) in THF (7.5 mL), prepared as described above, was added dropwise a solution of lactone **16b** (0.30 g, 0.76 mmol) in THF (2 mL). The mixture was stirred at −78 °C for 20 min, and then freshly distilled benzyl iodide (0.18 g, 0.84 mmol) in THF (1 mL) was added over 2 min. The ensuing reaction mixture was stirred at −78 °C for 30 min and then quenched with aqueous phosphate buffer (pH 7, 10 mL) and allowed to warm to rt over 15 min. The mixture was treated with EtOAc (9 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 9 mL), and the combined organic phases were dried ($Na_2SO_4$) and concentrated. Flash chromatography on silica gel of the residue (7:3 hexane–$Et_2O$) afforded pure **20b** (0.3 g, 81%) as a white solid: mp 123–125 °C; $[\alpha]_D$ −23.3 (*c* 1.3, $CHCl_3$); $^1H$ NMR (DMSO-$d_6$, 100 °C) $\delta$ 1.31 (s, 9 H), 1.95–2.12 (m, 2 H), 2.76 (dd, 1 H, $J$ = 8.5, 13.0 Hz), 2.78–2.95 (m, 3 H), 2.99 (dd, 1 H, $J$ = 4.9, 13.0 Hz), 4.18 (d, 1 H, $J$ = 15.6 Hz), 4.13–4.23 (m, 1 H), 4.27 (d, 1 H, $J$ = 15.6 Hz), 4.58 (ddd, 1 H, $J$ = 5.8, 7.8, 8.5 Hz), 7.08–7.32 (m, 15 H). Anal. Calcd for $C_{31}H_{35}NO_4$: C, 76.68; H, 7.26; N, 2.88. Found: C, 76.79; H, 7.35; N, 2.94.

**(3*R*,5*S*,1′*S*)-3-Benzyl-5-[1′-(*N*-Benzylamino)-2′-phenylethyl]dihydrofuran-2(3*H*)-one (21b).** The lactone **20b** (0.25 g, 0.51 mmol) was processed as described above for **17a** to give the crude product **21b** (0.18 g, 93%; 95% pure by $^1H$ NMR) which was immediately used for the next reaction without further purification: $^1H$ NMR $\delta$ 1.84 (ddd, 1 H, $J$ = 7.9, 8.8, 12.7 Hz), 1.99 (ddd, 1 H, $J$ = 4.4, 9.5, 12.7 Hz), 2.60 (ddd, 1 H, $J$ = 2.6, 5.8, 9.1 Hz), 2.69 (dd, 1 H, $J$ = 9.1, 13.2 Hz), 2.74 (dd, 1 H, $J$ = 9.3, 14.0 Hz), 2.95 (dd, 1 H, $J$ = 5.8, 13.2 Hz), 3.18 (dd, 1 H, $J$ = 4.3, 14.0), 3.26 (dddd, 1 H, $J$ = 4.3, 7.9, 9.3, 9.5 Hz), 3.65 (d, 1 H, $J$ = 13.1 Hz), 3.86 (d, 1 H, $J$ = 13.1 Hz), 4.22 (ddd, 1 H, $J$ = 2.6, 4.4, 8.8 Hz), 7.10–7.35 (m, 15 H); $^{13}C$ NMR $\delta$ 29.9, 36.8, 37.3, 41.4, 51.8, 61.6, 77.8, 126.7, 126.9, 127.4, 128.6, 128.7, 128.9, 129.1, 129.6, 138.6, 138.8, 140.2, 180.2.

**(3*R*,5*S*,1′*S*)-3-Benzyl-5-[1′-[*N*-(*tert*-butoxycarbonyl)amino]-2′-phenylethyl]dihydrofuran-2(3*H*)-one (1b).** The lactone **21b** (0.18 g, 0.47 mmol), was hydrogenated as described above for **19a**. Flash chromatography on silica gel of the crude residue (85:15 toluene–$Et_2O$) gave pure **1b** (0.13 g, 71%) as a white solid: mp 78–80 °C; $[\alpha]_D$ −16.5 (*c* 1.2, $CHCl_3$) (lit.[11] mp 76–78 °C; lit.[12] mp 89–91 °C; $[\alpha]_D$ −17.3 (*c* 1.2, $CHCl_3$)); $^1H$ NMR $\delta$ 1.35 (s, 9 H), 1.89–2.02 (m, 1 H), 2.12–2.29 (m, 1 H), 2.77 (dd, 1 H, $J$ = 8.1, 14.1 Hz), 2.80–2.90 (m, 2 H), 2.90–3.05 (m, 1 H), 3.12 (dd, 1 H, $J$ = 5.0, 14.1 Hz), 3.87–4.0 (m, 1 H), 4.16–4.25 (m, 1 H), 4.55 (d, 1 H, $J$ = 10.1 Hz), 7.10–7.30 (m, 5 H); $^{13}C$ NMR $\delta$ 27.7, 36.4, 38.6, 40.9, 54.1, 78.0, 79.8, 95.9, 126.8, 126.9, 128.7, 128.8, 128.9, 129.3, 137.1, 137.9, 155.0, 179.5. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.88; H, 7.39; N, 3.54. Found: C, 72.59; H, 7.60; N, 3.22.

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