Allyltrichlorostannane Additions to α-Amino Aldehydes: Application to the Total Synthesis of the Aspartyl Protease Inhibitors L-682,679, L-684,414, L-685,434, and L-685,458

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This paper is dedicated to Prof. Albert Kascheres on the occasion of his 60th birthday and also to the Brazilian Chemical Society (SBQ).

Abstract: The hydroxyethylene dipeptide isosteres L-682,679, L-684,414, L-685,434, and L-685,458 were synthesized in a few steps by a sequence involving an allyltrichlorostannane coupling with an α-amino aldehyde, followed by hydroboration of the corresponding 1,2-*syn* and 1,2-*anti* amino alcohols to give the diols, lactonization under TPAP conditions, lactone opening, and peptide coupling with the desired amine or dipeptide amide. The present synthetic approach represents a practical entry to a large range of other dipeptide isosteres.

Key words: amino aldehydes, HIV, peptides, total synthesis, lactones

Introduction

In the last several years there have been major research efforts towards the development of clinically useful inhibitors of aspartyl proteases.[1–7] This worldwide search has led to various peptide isosteres, wherein the scissile peptide bond is replaced by a hydrolytically more stable isosteric functional group. In this context, the hydroxy amino acid framework **B** (Figure 1), where the peptide linkage of the sequence in structure **A** is replaced by a $CH(OH)CH_2$ group, constitutes a useful class of aspartyl protease inhibitors.[1–7]

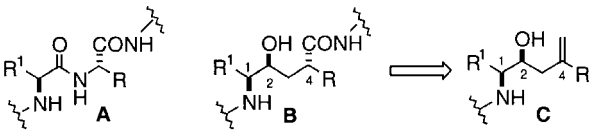

Figure 1 Core units of HIV protease inhibitors

HIV-1 Protease Inhibitors

The acquired immunodeficiency syndrome (AIDS) remains a serious public problem, especially in developing countries where it has now reached tragic dimensions and treatment is affordable only for a small percentage of infected people. The HIV virus, the causative agent of AIDS, is a highly mutable lentivirus, a member of the retrovirus family *Retroviriadae*, whose genome is encoded in RNA. Success in the development of HIV-Protease inhibitors as drugs was based upon early recognition of the central role of this enzyme in viral maturation and an intensive effort toward gaining an understanding of its structure and function.[1–7] L-685,434 (**1**) is a potent HIV-1 protease inhibitor (IC_{50} = 0.23 nM) containing (1*S*,2*R*)-1-amino-2-hydroxyindan P_2' ligand (Figure 2).[8,9] This inhibitor was found to block the spread of HIV-1 in T-lymphoid cells, being a highly potent and selective HIV protease inhibitor.

The pseudo pentapeptide L-682,679 (**2**) is a highly potent and selective inhibitor of HIV-1 protease (IC_{50} = 0.42 nM, Figure 2).[10] Structural manipulations of various portions of this molecule provided compounds with enhanced potency, selectivity, and solubility.

γ-Secretase Inhibitors

Alzheimer's disease (AD), a physical disease which attacks brain cells, nerves and transmitters, is the most common cause of dementia.[11–15] New drugs are being developed which seek to slow down the rate of mental decline, but they are promising only in the early stages of the disease. β-Secretase inhibitors are already under development and inhibition of amyloid β-peptide (Aβ) production is the desired goal. Compounds that would inhibit either β- or γ-secretase could potentially block Aβ production and be useful in treating Alzheimer's disease.[11–15] L-685,458 (**3**) is a potent inhibitor of γ-secretase (IC_{50} = 17nM) and is of potential therapeutic benefit in the treatment of Alzheimer's disease and other neurological disorders (Figure 2).[16–18] This compound, originally developed as an HIV protease inhibitor, was found to be a poor inhibitor of HIV protease, but a potent inhibitor of γ-secretase. L-685,458 (**3**) is a novel inhibitor of AβPP-γ-secretase activity, with a similar potency for inhibition of Aβ(42) and Aβ(40) peptides. Elevated levels of Aβ(42) peptide formation have been linked to early onset of familiar AD-causing gene mutations in the amyloid β-protein precursor (AβPP) and the presenilins. Sequential cleavage of AβPP by β- and γ-secretase generates the N- and C- termini of the Aβ peptide, making both the β- and γ-secretase enzymes potential therapeutic targets for AD.[16–18] L-685,458 (**3**) contains a hydroxyethylene dipeptide isostere that should serve as a transition state

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Biographical Sketches

Luiz Carlos Dias was born in 1964, in Balneário Camboriú, SC (Brazil). He received his undergraduate degree from the Federal University of Santa Catarina (UFSC), Florianópolis, SC, in 1988. He received his PhD, in 1993 with a thesis on alkaloid chemistry developed under the supervision of Prof. R. A. Pilli, at the State University of Campinas (UNICAMP). In 1992 he joined the faculty at the Department of Chemistry at UNICAMP as an Instructor. In 1993 he was promoted to Assistant Professor and in 1999 to Associate Professor. He spent two years as a postdoctoral fellow with Prof. David A. Evans at Harvard University, USA (1994–1995) where he worked on the total synthesis of spongistatin A.
His research interests lie in the study of the control elements that influence the stereochemical outcome of double stereodifferentiating chiral allylsilane, allylstannane and methyl ketone additions to chiral aldehydes and imines. These methodological studies are being applied to the asymmetric synthesis of a wide variety of important natural and synthetic products of biological significance. Short, efficient and flexible synthetic routes to biologically important compounds like HIV-1 inhibitors, immunosuppressant agents, plant toxins, herpes virus inhibitors, antibiotics, antitumor agents and neurotransmitters are being developed in his laboratory.
In 1999, Prof. Dias received the Journal of the Brazilian Chemical Society Medal (http://jbcs.sbq.org.br/) and since 2000 he is the General Secretary of the Brazilian Chemical Society (SBQ). Most of the rest of his time is spent with his wife Luciana and two daughters, Luana and Luiza.
(Further informations: http://pc-server.iqm.unicamp.br/~ldias)

Gaspar Diaz Muñoz was born in 1964 in Iquitos (Peru) and received his undergraduate degree in chemical engineering in 1989 from the National University of Peruvian Amazon (UNAP). He then moved to Brazil and obtained his Masters degree in 1997 at the Federal University of Pará (UFPA) under the supervision of Prof. Alberto C. Arruda. He obtained a PhD in chemistry from the State University of Campinas (UNICAMP) in 2001, under the supervision of Prof. Fernando A. S. Coelho, working on the synthesis of (+/-)-Pathylactone A, a nor-sesquiterpene lactone isolated from marine sources. In 2002 he joined the research group of Prof. Dias as a postdoctoral fellow. Gaspar now resides with his wife Marisa, and their son Flávio, in Cascavel, (Brazil).

Andréa A. Ferreira was born in 1975 in São Paulo, SP (Brazil) and received her undergraduate degree in chemistry at the State University of Campinas (UNICAMP) in 1998. As an undergraduate she carried out research in the group of Prof. Dias and then obtained her Masters degree, in 2002, from the State University of Campinas under the supervision of Prof. Dias. Andrea and her husband, Wagner, are now expecting their first daughter, Beatriz, which should be born in March, 2003.

Paulo R. R. Meira was born in 1966 in Goiânia, GO (Brazil) and obtained a Bachelor's degree in chemistry at the Federal University of Goiás (1993). In 1997, Paulo and his wife Gêmia, moved to Campinas and Paulo joined the research group of Prof. Dias at the State University of Campinas (UNICAMP). He finished his Masters degree in 1999 and he is currently pursuing his PhD under the direction of Prof. Dias. His research focuses on studies towards the total synthesis of callystatin A, a potent antitumor polyketide isolated from the marine sponge Callyspongia truncata.

Edílson Ferreira was born in 1974 in Elói Mendes, MG (Brazil) and obtained his undergraduate degree in chemistry at the State University of Campinas (UNICAMP) in 1998. As an undergraduate student he joined the research group of Prof. Dias at the State University of Campinas and finished his Masters degree in 2001. Edílson now resides with his wife Adriana and their son Davi, in Elói Mendes, MG. He is currently teaching organic chemistry at the University of Alfenas (UNIFENAS) and centro Universitário do Sul de Minas (UNIS), Minas Gerais State, Brazil.

analogue mimic to direct the inhibitor to the active site of an aspartyl protease target (Figure 2). L-684,414 (**4**), the ketone derivative, was also found to be active (IC_{50} = 181 nM) but less so than L-685,458 (**3**), as expected if the hydroxyethylene dipeptide is serving as a transition state mimic. The observations that the inhibitory potency of L-685,458 (**3**) is sensitive to the configuration of the hydroxylic carbon atom and that the substrate analogue L-682,679 (**2**) is processed by γ-secretase (IC_{50} >10000 nM) and binds to the enzyme much less tightly than L-685,458 (**3**) provide strong evidence that L-685,458 (**3**) is an active site directed transition state analogue inhibitor for an aspartyl protease. This supports the conclusion that γ-secretase is an aspartyl protease and agrees with previous studies showing that other aspartyl protease transition state analogues inhibit γ-secretase activity in cells.[11–18]

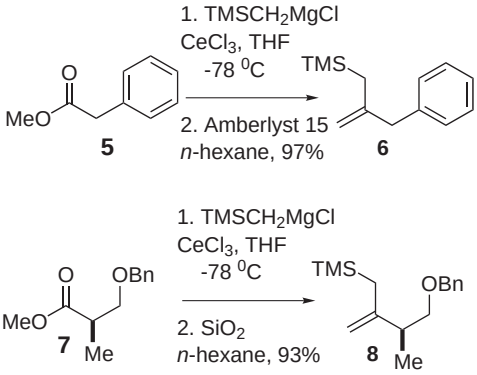
Based on our initial results on allyltrichlorostannane additions to *N*-Boc-α-amino aldehydes and attracted by the highly potent inhibition of AβPP γ-secretase activity of L-685,458 (**3**), as well as by the HIV inhibitory potency of **1**, **2** and **4**, we initiated a project directed towards their total synthesis. An efficient and flexible synthesis is essential to provide material for more extensive biological studies, along with access to novel analogues. The approach described here to L685,434 (**1**), L-682,679 (**2**), L-685,458 (**3**), and L-684,414 (**4**) might also give access to additional derivatives with potential relevance for biological evaluation.

Results and Discussion

Allylsilane Additions to N-Boc-α-amino Aldehydes

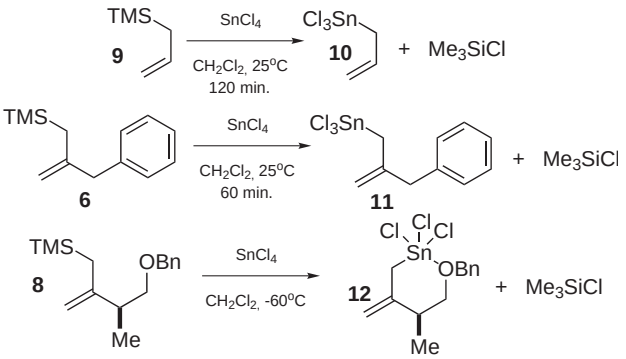
We began this work a few years ago, and observed that allylsilanes react with *N*-Boc-α-amino aldehydes in the presence of $SnCl_4$ to give 1,2-*syn* *N*-Boc-α-amino alcohols that are key intermediates (molecules of type **C**, Figure 1) for the preparation of hydroxyethylene dipeptide isosteres.[19–25] We have also reported the first successful examples of allylsilane additions to chiral dipeptide aldehydes.[24] This synthetic methodology allows compounds with programmed variations of substituents to be synthesized and is particularly important in the screening of the pharmacological activity and in the study of structure-activity relationships directed toward the design of the best substituents for positions 1 and 4 in structure **C** (R^1 and R groups, Figure 1).

In order to prepare these allylsilanes, the cerium reagent generated from cerium(III) chloride and trimethylsilylmethylmagnesium chloride was reacted with methyl ester **5** to give an intermediate bis(trimethylsilylmethyl)carbinol which, after treatment with amberlyst 15® in *n*-hexane, gave allylsilane **6** in 97% yield for the two-step sequence (Scheme 1).[26,27] Treatment of methyl ester **7** under the same conditions gave an intermediate carbinol that was treated with silica gel in hexane to give allylsilane **8** in 93% yield for the two-step sequence.[19]



Scheme 1 Preparation of allylsilanes **6** and **8**

The next step involved a spectroscopic study (^1H, ^{13}C, and ^{119}Sn NMR) of the reactions of allylsilanes **6**, **8** and **9** with $SnCl_4$ (Scheme 2). Allylsilanes **6**, **8** and **9** and $SnCl_4$ (0.5 M solution in $CDCl_3$) were mixed in order to promote ligand exchange, leading to the corresponding allyltrichlorostannanes.[22] For allyltrimethylsilane (**9**) (0.5 M in $CDCl_3$) the ligand exchange producing allyltrichlorostannane (**10**) and Me_3SiCl is complete after 120 minutes at room temperature (Scheme 2). For allylsilane **6** (0.5 M in $CDCl_3$) the metathesis to give **11** and Me_3SiCl is faster, as expected for a 1,1-disubstituted olefin, being complete after 60 minutes at room temperature.[22] Upon addition of $SnCl_4$ to a solution of chiral allylsilane **8** in $CDCl_3$, at –60 °C, as well as at 25 °C, a slightly yellow homogeneous solution was obtained. The resulting NMR spectra at –60 °C showed the formation of Me_3SiCl and complete consumption of the allylsilane **8** within 1 minute to give allyltrichlorostannane **12**. It appears that the oxygen functionality is responsible for the rapid ligand exchange reaction observed even at low temperatures for this particular allylsilane and $SnCl_4$. The ligand exchange reaction is probably facilitated by coordination of tin to this oxygen followed by cleavage of the carbon–silicon bond by a free chloride ion.



Scheme 2 Metathesis of allylsilanes **6**, **8** and **9**

We have observed ^{119}Sn resonance signals at –27 ppm for allylstannanes **10** and **11**. The tin chemical shift for allylstannane **12** appeared at –187 ppm. We believe that tin chemical shifts are highly sensitive to oxygen bonding,

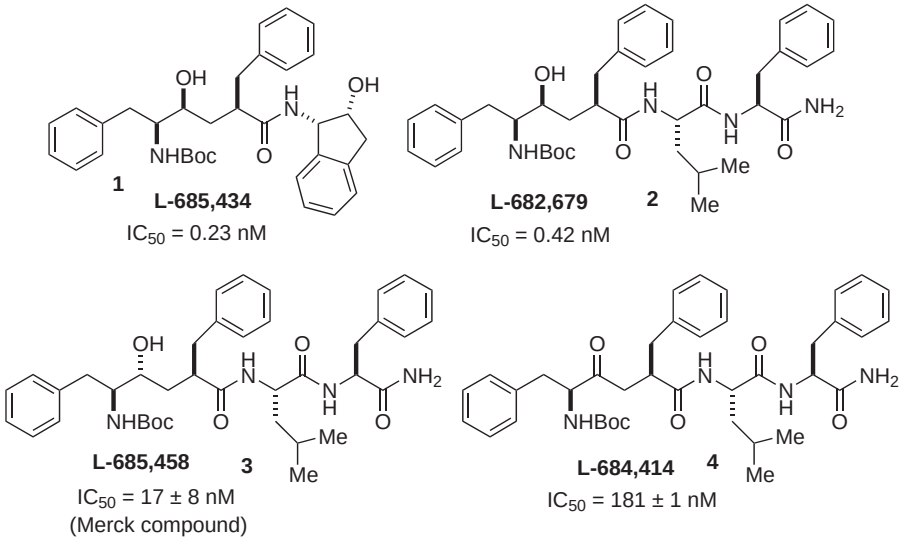
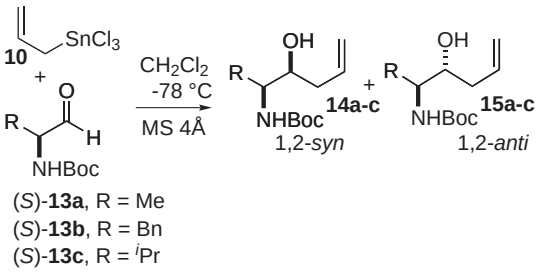


Figure 2 Chemical structures of the inhibitors L-685,434, L-682,679, L-685,458 and L-684,414

and this is an observation in favor of the complexed intermediate.

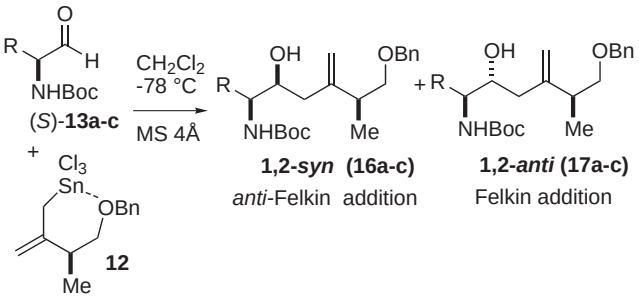
We next moved to investigate the allyltrichlorostannane additions to chiral aldehydes **13a**–**c**. In order to confirm the facial selectivities of the (*S*)-*N*-Boc-α-amino aldehydes **13a**–**c**, we reacted them with allyltrichlorostannane **10** (Scheme 3, Table 1).[19–25]



Scheme 3 Allyltrichlorostannane addition to α-amino aldehydes **13a**–**c**

In all cases, the major product results from a chelation-controlled reaction that mainly gives the 1,2-*syn*-isomers **14a**–**c**, showing that the (*S*)-α-amino aldehydes **13a**–**c** have a preference for *anti*-Felkin addition (*Si* face attack).[28,29] The increased steric bulk of the R group gives better diastereoselection.[1d,28–31]

Under the same conditions, chiral allyltrichlorostannane **12** reacted with (*S*)-α-amino aldehydes **13a**–**c** to give a mixture of 1,2-*syn* (**16a**–**c**) and 1,2-*anti* (**17a**–**c**) diastereomers with useful diastereoselectivities, favoring the 1,2-*syn*-isomer with *anti*-Felkin addition and aldehyde *Si* face attack (Scheme 4). Results of reactions of **12** with (*S*)-aldehydes **13a**–**c** are summarized in Table 2.[19–25]



Scheme 4 Chiral allyltrichlorostannane addition to α-amino aldehydes **13a**–**c**

As we know from previous work that the chiral allyltrichlorostannane **12** has a preference for *Si* face ap-

Table 1 Allyltrichlorostannane Addition to (*S*)-*N*-Boc-α-amino Aldehydes **13a**–**c**

13a (R = Me)[a,b]	Yield	**13b** (R = Bn)[a,b]	Yield	**13c** (R = *i*-Pr)[a,b]	Yield
1,2-*syn* : 1,2-*anti*	(%)[c]	1,2-*syn* : 1,2-*anti*	(%)[c]	1,2-*syn* : 1,2-*anti*	(%)[c]
88:12	85	90:10	86	90:10	85

[a] The ratios were determined by ^{1}H and ^{13}C NMR spectroscopic analysis of the purified product mixture. The 1,2-*syn*- and *anti*-products could not be separated and were characterized as mixtures.
[b] Averages of at least three runs with ratios ±3%.
[c] Combined yields of products isolated chromatographically (silica gel), after 2 steps (reduction to the aldehyde and coupling with allyltrichlorostannane).

Table 2 Tin(IV) Chloride-Promoted Additions of Chiral Allyltrichlorostannane **12** to (*S*)-*N*-Boc-α-Amino Aldehydes

13a (R = Me)[a,b]	Yield	**13b** (R = Bn)[a,b]	Yield	**13c** (R = *i*-Pr)[a,b]	Yield
1,2-*syn*:1,2-*anti*	(%)[c]	1,2-*syn*:1,2-*anti*	(%)[c]	1,2-*syn*:1,2-*anti*	(%)[c]
95:05	88	95:05	84	95:05	85

[a] The ratios were determined by ^{1}H and ^{13}C NMR spectroscopic analysis of the purified product mixture. The 1,4-*syn* and *anti*-products could not be separated and were characterized as mixtures.
[b] Averages of at least three runs with ratios ±3%.
[c] Combined yields of products isolated chromatographically (silica gel), after 2 steps (reduction to the aldehyde and coupling with allyltrichlorostannane).

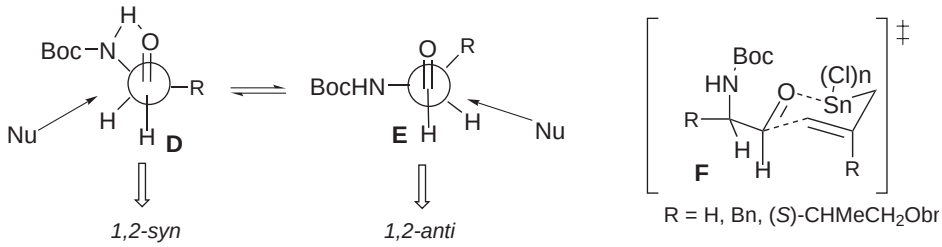
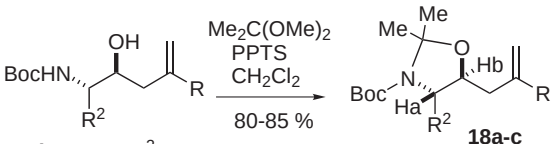


Figure 3 Transition state model

proach, this is an example of a *matched* reaction.[19] It should be noted that this reaction gives a very important subunit with a double bond and a benzyl protected primary alcohol that can be further manipulated.[32,33]

The 1,2-*syn* relative stereochemistry of the major products was unambiguously established by spectroscopic analysis of the corresponding *trans*-oxazolidines **18a**–**c** (upon irradiation of the hydrogens adjacents to H_a and H_b). Observed average coupling constants (^3J = 1.0 to 4.6 Hz) indicate that protons H_a and H_b are on opposite faces of the heterocyclic ring, and therefore, the oxazolidines are derived from 1,2-*syn* adducts (Scheme 5).[34]



14b, R = H, R^2 = Bn
16a, R = CH(Me)CH_2OBn, R^2 = Me
16c, R = CH(Me)CH_2OBn, R^2 = ^{i}Pr

	$J_{Ha/Hb}$ *trans*	$J_{Ha/Hb}$ *cis*
Literature:	1.1-4.9 Hz	4.6-6.0 Hz
Observed:	1.0 to 4.6 Hz	

Scheme 5 Coupling constant analysis

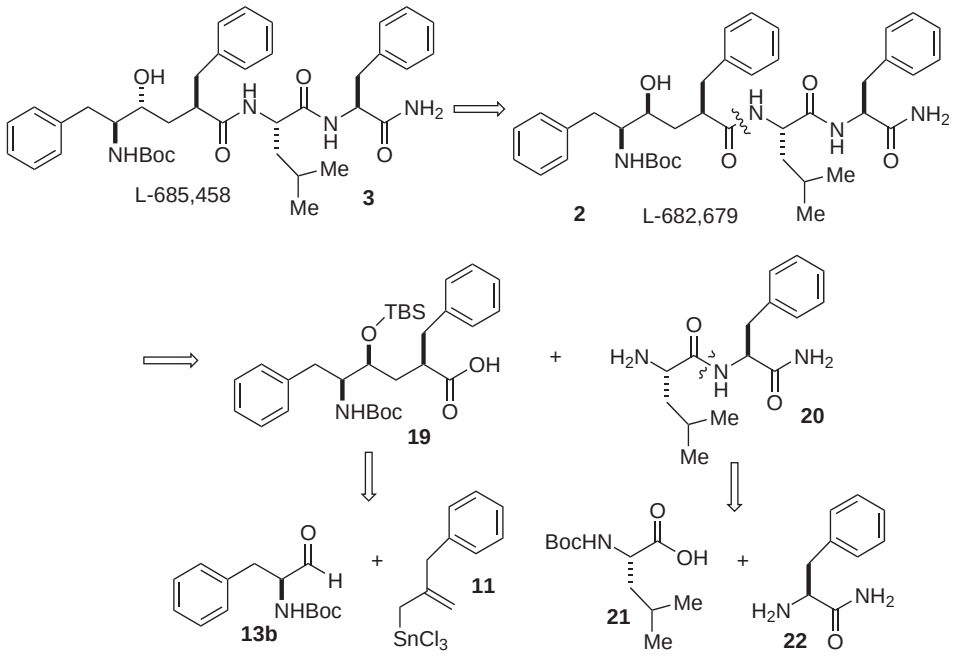
The stereoselectivity of these reactions is consistent with a mechanism involving transmetalation of the allylsilanes to give an intermediate allyltin trichloride.[22,35] We expect such reactions to be dominated by the stereogenic center next to the aldehyde function. We believe that the observed selectivity can be explained by an equilibrium between the intramolecular hydrogen bond conformer **D** and the non-bonded conformer **E** (Figure 3).[36] When the form **D** predominates (bulkier R groups), the *syn*-isomer is favored, whereas the prevalence of the **E**-like conformer (smaller R groups) leads to the *anti*-isomer. The nucleophile selects the less hindered Si-face, forming a six membered transition state **F** where the chiral residue of the aldehyde occupies a pseudo-equatorial position.

Total Synthesis of Aspartyl Protease Inhibitors L-682,679, L-684,414, L-685,434, and L-685,458

Our disconnection for the synthesis of compounds **2**–**4** is illustrated for inhibitor **3**, summarized in Scheme 6. Not surprisingly, compound **3** is viewed as arising from **2** by either alcohol oxidation followed by selective 1,2-*anti* reduction[37] or by using the Mitsunobu inversion protocol.[38] Further analysis involved cleavage of the C–N peptide bond to give fragments **19** and **20**. Carboxylic acid **19**, the core unit common for the synthesis of compounds **1**–**4**, is viewed as arising from α-amino aldehyde **13b** by selective allyltrichlorostannane addition followed by hydroboration of the double bond and oxidation of the resulting primary alcohol. Dipeptide **20** may be dissected in a straightforward manner to give carboxylic acid **21** and amide **22**.

Our approach to aspartyl protease inhibitors **1**–**4** began with *N*-Boc-phenylalaninal (**13b**), a useful synthetic intermediate, easily prepared from α-phenylalanine ethyl ester by Boc protection followed by DIBALH reduction.[28–33]

According to a previously established experimental procedure, allylsilane **6** and $SnCl_4$ (0.5 M solution in CH_2Cl_2) were mixed before the addition of a solution of the aldehyde in order to promote in situ ligand exchange, leading to the corresponding allyltrichlorostannane **11** (Scheme 2).[19–25] Addition of the aldehyde **13b** to a CH_2Cl_2 solution of allyltrichlorostannane **11** at –78 °C gave the 1,2-*syn* amino alcohol **23** in 94% yield for the two-step se-



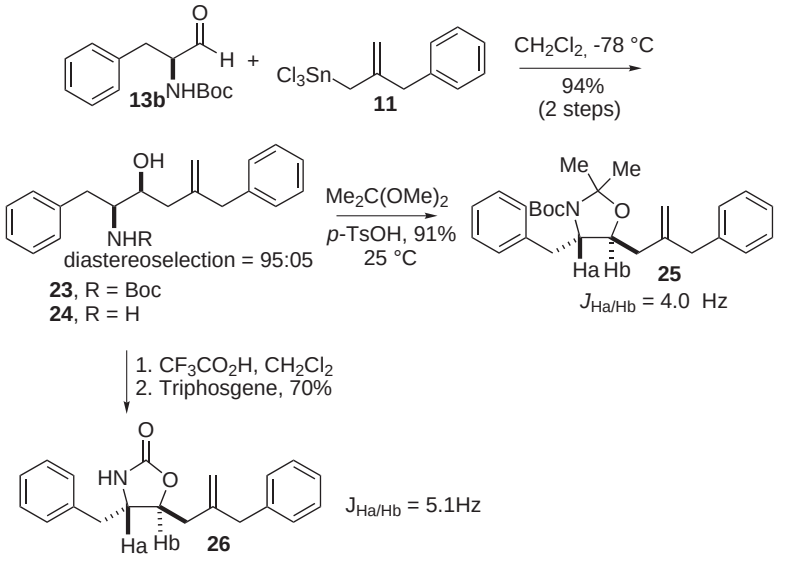
Scheme 6 Retrosynthetic analysis

quence (DIBALH reduction of α-phenylalanine ethyl ester and coupling with allyltrichlorostannane) and 95:5 diastereoselectivity (Scheme 7).[28–33]

The ratio was determined by ^{1}H and ^{13}C NMR spectroscopic analysis of the crude mixture, with averages of at least three runs with ±3% accuracy.

It is essential to promote the ligand exchange reaction before addition of the aldehyde in order to get good yields and selectivities. This reaction benefits from the fact that the real nucleophile is the allyltrichlorostannane and not the allylsilane itself. If the allyltrichlorostannane addition reaction is carried out from –78 °C to room temperature, we have observed loss of the Boc protecting group with the corresponding deprotected homoallylic alcohol **24** being isolated in 82% yield and having essentially the same selectivity.

The next step involved treatment of amino alcohol **23** with $Me_2C(OMe)_2$ in the presence of catalytic amounts of *p*-TsOH to give *trans* oxazolidine **25** in 91% yield after purification by silica gel column chromatography.[39,40] The 1,2-*syn* relative stereochemistry was unambiguously established by spectroscopic analysis of *trans* oxazolidine **25** (upon irradiation of the hydrogens adjacent to Ha and Hb). The observed coupling constant ($J_{Ha/Hb}$ = 4.0 Hz) in-



Scheme 7 Coupling between allyltrichlorostannane **11** and aldehyde **13b**

dicated that hydrogens Ha and Hb are on opposite faces of the heterocyclic ring and, therefore, the oxazolidine is derived from 1,2-*syn* adduct (Scheme 7).[34,39,40] Alternatively, amino alcohol **24** was transformed to the corresponding oxazolidinone **26** (70%), followed by ^{1}H NMR coupling constant analysis. The observed coupling constant ($J_{Ha/Hb}$ = 5.1 Hz) indicates that hydrogens Ha and Hb are on opposite faces of the heterocyclic ring (Scheme 7).

The double bond in acetonide **25** was oxidatively hydroborated at 0 °C with $BH_3{\cdot}SMe_2$ to give primary alcohols **27** and **28** in 93% overall yield (Scheme 8).[6,39–41] The use of the more hindered 9-BBN gave essentially the same result, although in lower yields (65%). Although these two isomers are not easily separated, we were able to get pure isolated compounds after careful silica gel flash column chromatography. A coupling constant of 4.0 Hz between H_a and H_b is again observed for alcohols **27** and **28**.[6,39–41]

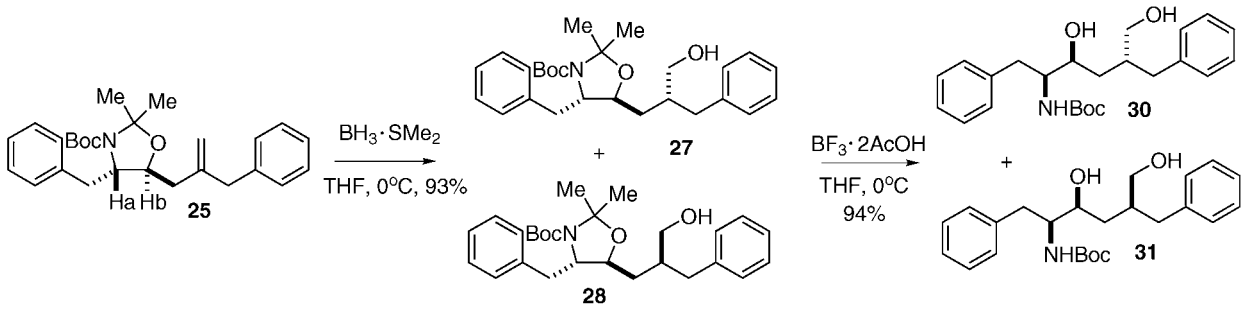
The relative stereochemistry for undesired primary alcohol **28** was ascertained by conversion to the piperidine derivative **29** after a two-step sequence involving reaction with Ph_3P, I_2 and imidazole, and treatment of the intermediate iodide with 4 M HCl in MeOH followed by K_2CO_3 in DMF (Scheme 9). The illustrated NOESY interactions confirmed the proposed relative stereochemistry for cyclic amino alcohol **29**.

Selective acetonide deprotection in alcohols **27** and **28** was achieved by using the complex $BF_3{\cdot}2AcOH$ at room temperature to give diols **30** and **31** (not separated by silica gel column chromatography) in 94% overall yield (Scheme 8). A better approach to these diols involved direct hydroboration of the unprotected homoallylic alcohol **23** with $BH_3{\cdot}SMe_2$ in THF at 0 °C to give a mixture of diols **30** and **31** in 93% yield (Scheme 10).

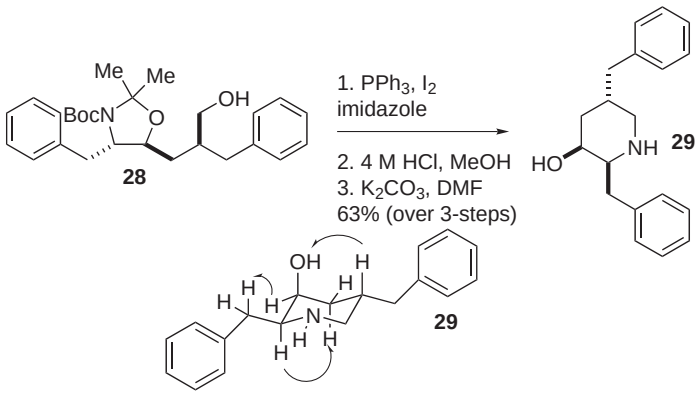
These diols were not separated but were converted directly to a mixture of lactones **32** and **33** (95% yield) by treatment with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholino *N*-oxide (NMO) in the presence of molecular sieves at room temperature.[42,43] These lactones were readily separated by flash column chromatography. Although these lactones have been prepared earlier by others, the relative stereochemistry for *cis*-lactone **33** was ascertained by NOESY experiments (observed interaction between H_a and H_b). Attempts to obtain more of the desired *trans*-lactone **32** by a deprotonation and reprotonation sequence of *cis*-lactone **33** led to a 70:30 mixture of lactones **32**:**33** in 96% yield (Scheme 10). It is interesting to point out that *cis*-lactone **33** is also an important intermediate for the synthesis of other potent HIV-1 protease inhibitors.[43b]

Basic hydrolysis of desired *trans*-lactone **32** (LiOH, 1,2-dimethoxyethane), silylation (TBSCl, imidazole, DMF, r.t., 12h) of the resulting carboxylate, and selective desilylation of the acylsiloxy moiety (MeOH) cleanly provided **19** in excellent yield after purification by silica gel flash chromatography (Scheme 11).

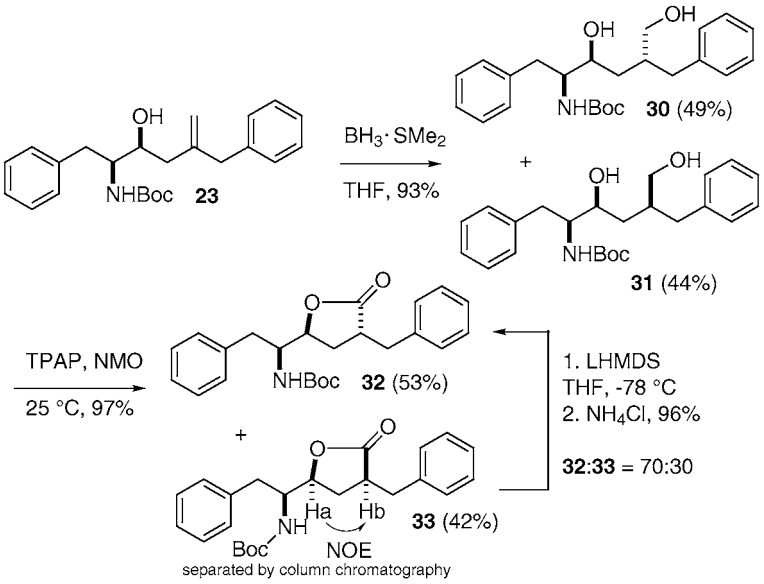
The carboxylic acid **19** is a versatile intermediate for the introduction of different functional groups in intermedi-



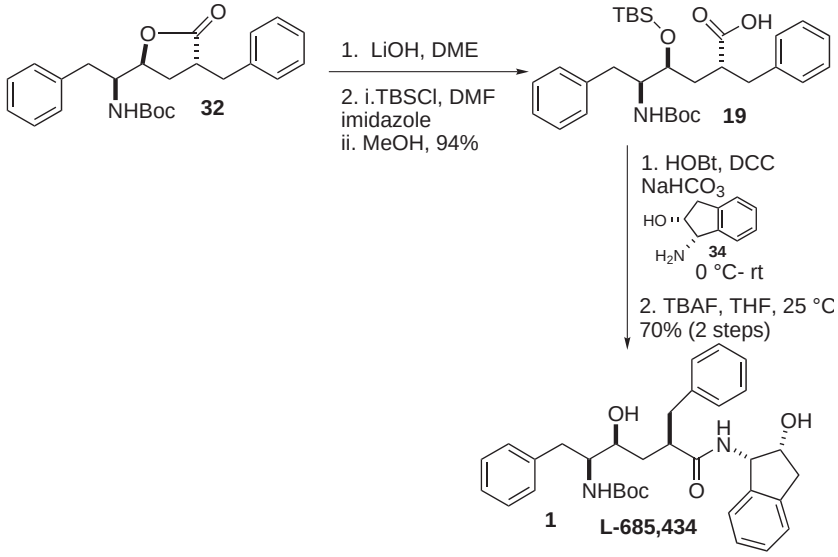
Scheme 8 Hydroboration of compound **25**



Scheme 9 Preparation of piperidine derivative **29**



Scheme 10 Direct hydroboration of homoallylic alcohol **23**



Scheme 11 Synthesis of L-685,434

ates aiming at the synthesis of hydroxyethylene isosteres and is prepared in 4 steps and 24% overall yield from **23**, being amenable to a gram scale-up.

Compound L-685,434 (**1**) is readily prepared from carboxylic acid **19** by a simple peptide coupling reaction with (1*S*,2*R*)-1-amino-2-hydroxyindane (**34**) followed by TBS removal with TBAF in 70% yield for the two-step sequence (Scheme 11).[6–8]

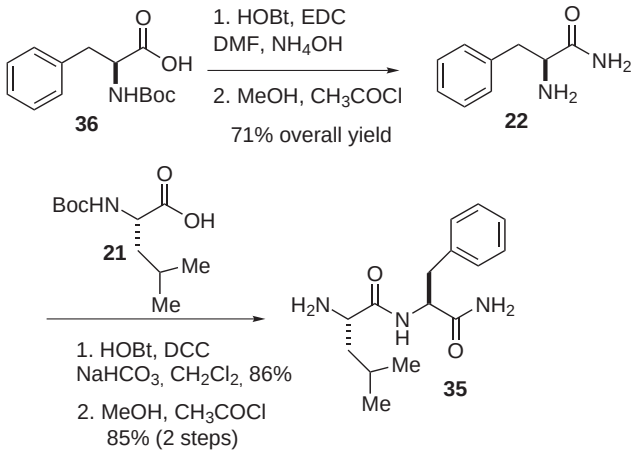
Compounds **2**–**4** are also prepared from the same carboxylic acid precursor **19**. In order to prepare inhibitors **2** and **3** we first obtained the dipeptide amide NH_2Leu-PheNH_2 (**35**) (Scheme 12). Peptide type coupling of *N*-Boc-phenylalanine (**36**) with a 25% solution of ammonium hydroxide followed by Boc deprotection with MeOH/AcCl gave amide **22** in 71% overall yield.

Peptide coupling between carboxylic acid **21** and amide **22**, followed by Boc deprotection, gave NH_2Leu-PheNH_2 **35** in 85% overall yield (Scheme 13).

Compound L-682,679 (**2**) is readily prepared from carboxylic acid **19** and dipeptidic amine **35** by a simple peptide coupling reaction followed by TBS deprotection with TBAF in 86% overall yield (Scheme 13).[10]

Oxidation of the hydroxyl function in **2** with pyridinium dichromate (PDC) in DMF gave inhibitor L-684,414 (**4**) in 85% isolated yield. Selective reduction of L-684,414 (**4**) with $LiBH_4$ gave γ-secretase inhibitor L-685,458 (**3**) in 93% yield and 95:5 diastereoselection (Scheme 13).[37]

Another approach to the synthesis of L-685-458 (**3**) is by using the corresponding 1,2-*anti* amino alcohol **39** prepared from **23**. Of the available options to promote the inversion of the hydroxyl stereochemistry of **23** in order to



Scheme 12 Preparation of NH_2Leu-PheNH_2 **35**

prepare L-685,458 (**3**) we tested the Mitsunobu reaction using 4-nitrobenzoic acid, Ph_3P and DBAD (Scheme 14).[38] The *p*-nitrobenzoate ester **37** was isolated in 60% yield together with about 10% of elimination product **38** and 20% of recovered starting material.

Hydrolysis of the 4-nitrobenzoate **37** with lithium hydroxide gave the desired 1,2-*anti* amino alcohol **39** in 98% yield (Scheme 14). Another approach for the preparation of **39** involved Dess–Martin[44] oxidation of **23** at 0 °C to give ketone **40** (77% yield) followed by $LiBH_4$[37] reduction in THF at –60 °C (Scheme 14). Although we were able to isolate the amino alcohol **39** in good yields and with 94:6 diastereoselectivity, this protocol is sometimes hard to reproduce since a lot of care must be taken in order to avoid rearrangement to the conjugated ketone **40**.

The 1,2-*anti* relative stereochemistry for **39** was tentatively assigned by spectroscopic analysis of the *cis*-oxazolidine **41** ($J_{Ha\text{-}Hb}$ = 4.7 Hz), (Scheme 14).[23–25,34] As the observed coupling constants for oxazolidines **25** (4.0 Hz) and **41** (4.7 Hz) were very close, we decided to check the differences in chemical shifts in compounds **23** and **39**. The relative stereochemistry for compounds **23** and **39** was confirmed using Heathcock's model for β-hydroxy carbonyl compounds (Scheme 15 and Table 3).[45] Considering an intramolecular hydrogen bond in $CDCl_3$ solution between NH and OH in both compounds, and after analysis of ^1H and ^{13}C NMR chemical shifts we observed that:

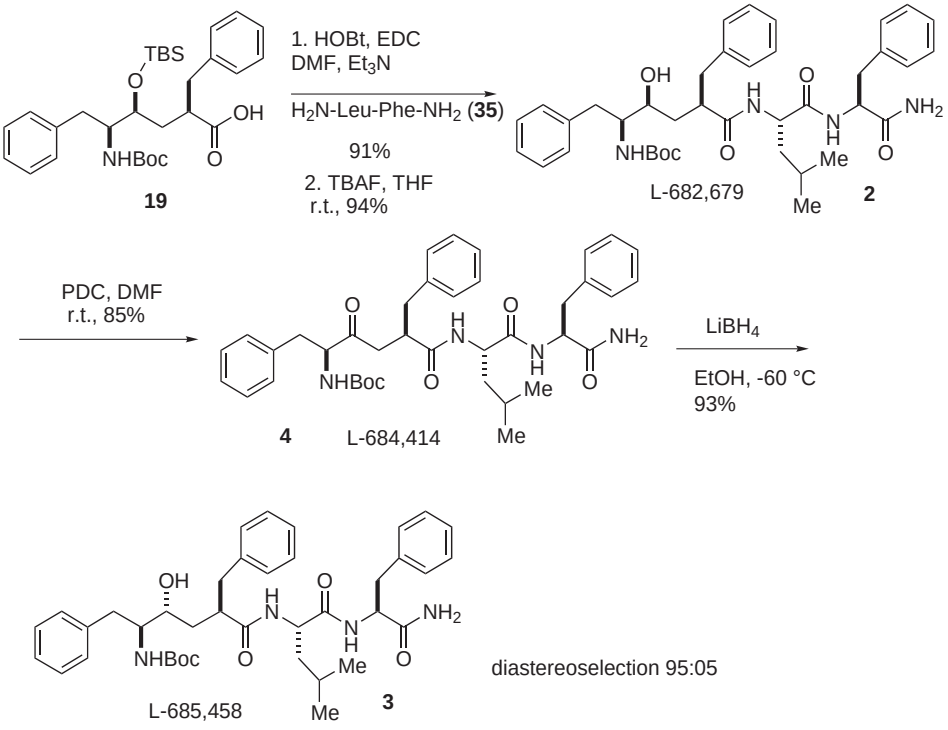
- C_1 and C_4 in **23** are more deshielded than C_1' and C_4' in **39**;

- C_2 and C_3 in **23** are more shielded than C_2' and C_3' in **39**; and

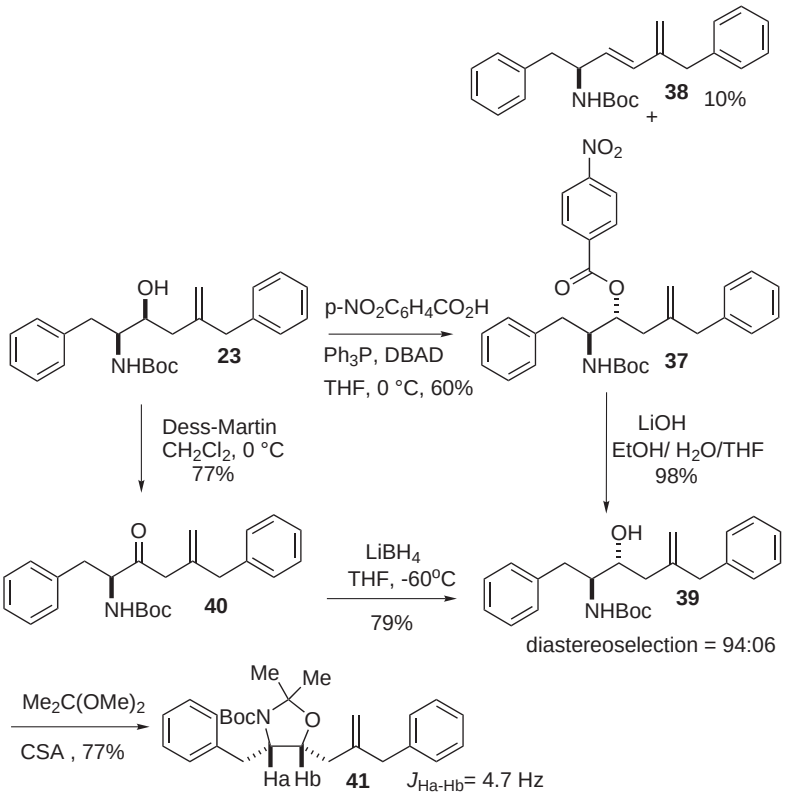
- Ha and Hb in **23** are more shielded than Hc and Hd in **39**.

It is also interesting to observe the difference in the melting points of compounds **23** and **39** (Scheme 15). The 1,2-*syn* amino alcohol **23**, where an intramolecular hydrogen bond between NH and OH is expected, leading to a *trans* relationship between the two substituents, has a melting point of 95.5–97.8 °C. The 1,2-*anti* amino alcohol **39**, where an intramolecular hydrogen bond in the solid state is not expected to be favored over intermolecular interaction, has a higher melting point (mp 141.5–142.3 °C). These results are consistent with the proposed stereochemistry for **23** and **39**.

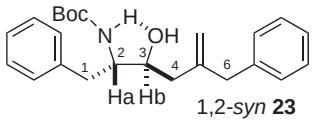
The next step involved a direct hydroboration of 1,2-*anti* homoallylic alcohol **39** with $BH_3{\cdot}SMe_2$ to give a 55:45 mixture of diols **42** and **43** in 93% overall yield



Scheme 13 Total synthesis of inhibitors **2**, **3** and **4**

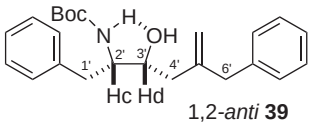


Scheme 14 Preparation of 1,2-*anti* amino alcohol **39**



1,2-*syn* **23**

m.p.: 95.5-97.8 °C



1,2-*anti* **39**

m.p.: 141.5-142.3 °C

Scheme 15 Spectroscopic data for compounds **23** and **39**

Table 3 Spectroscopic Data for Compounds **23** and **39**

1,2-*syn* **23**, δ		1,2-*anti* **39**, δ	
C1	38.9	C1′	35.5
C2	55.2	C2′	56.1
C3	68.1	C3′	71.1
C4	40.9	C4′	39.9
C6	42.7	C6′	42.8
Ha	3.67	Hc	3.80
Hb	3.67	Hd	3.80

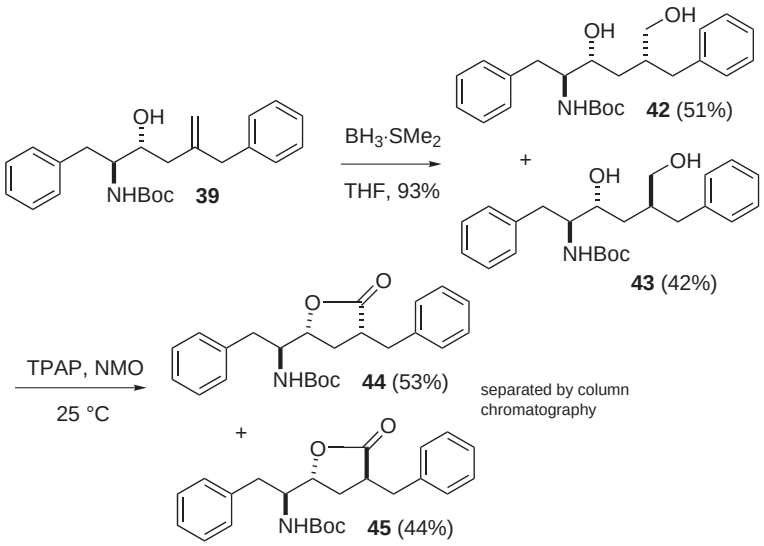
(Scheme 16). These diols were not separated but were most conveniently treated with TPAP to give a mixture of lactones **44** and **45** (97% overall yield), which were then separated by silica gel column chromatography.[18]

A two-step sequence involving opening lactone **44** with lithium hydroxide (5 equiv) in aqueous 1,2-dimethoxyethane followed by treatment of the resulting hydroxy acid with TBSCl and imidazole, in DMF at room temperature, followed by MeOH, gave the desired TBS-protected acid **46** in 73% overall yield (Scheme 17).[18] At this stage, all that remained was to carry out the necessary peptide coupling between **46** and **35** and remove the TBS protecting group.

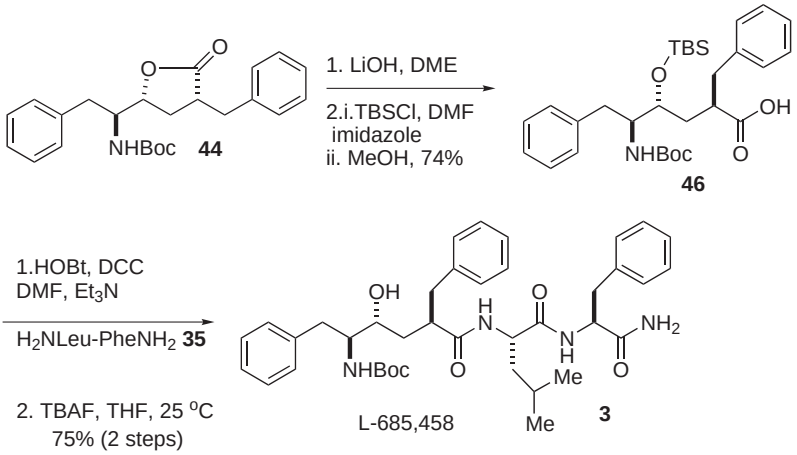
Compound **3** is thus prepared in 75% yield from **46** and NH_2Leu-PheNH_2 (**35**) by a simple peptide coupling reaction followed by deprotection of the resulting silyl ether with TBAF in THF at room temperature.[17,18,46] The spectroscopic and physical data [IR, ^{1}H and ^{13}C NMR; mp and R_f] for inhibitor **3** were identical in all respects with the published data. The observed optical rotation, $[\alpha]_D^{25}$ –27.5 (*c* = 0.5, $CHCl_3$) agrees satisfactorily with the reported value {$[\alpha]_D^{25}$ –27.9 (*c* = 0.5, $CHCl_3$)}.[18,46,47]

Conclusions

This convergent asymmetric approach to aspartyl protease inhibitors L-685,434 (**1**), L-682,679 (**2**), L-685,458 (**3**) and L-684,414 (**4**) relies on the use of amino alcohol **23** as a key intermediate. The route described here might



Scheme 16 Hydroboration of **39** followed by lactonization



Scheme 17 Synthesis of L-685,458

easily provide access to additional analogues with potential relevance in biological studies.

All reactions were carried out under argon or N_2 in flame-dried glassware with magnetic stirring. CH_2Cl_2, Et_3N, cyclohexane, and DMF were distilled from CaH_2. $SnCl_4$ was distilled from CaH_2 and stored in a Schlenk flask. DMSO was distilled under reduced pressure from CaH_2 and stored over molecular sieves. THF, Et_2O, and toluene were distilled from sodium/benzophenone ketyl. Oxalyl chloride, dimethoxypropane, isobutyraldehyde, trimethylsilylmethyl chloride and $(c\text{-Hex})_2BCl$ were distilled immediately prior to use. MeOH was distilled from $Mg(OMe)_2$. TLC plates were silica gel 60 (GF 5–40 μm). Visualization was accomplished with either a UV lamp or I_2 staining. Chromatography on silica gel (230–400 mesh) was performed using forced-flow of the indicated solvent system (flash chromatography). Visualization was accomplished with UV light and an anisaldehyde, ceric ammonium nitrate stain, a heated phosphomolybdic acid or by I_2 staining. ^{1}H NMR spectra were recorded on either a Varian Gemini 300 (300 MHz) or a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using residual undeuterated solvent as an internal standard ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.15 ppm), unless otherwise indicated. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, st = sextet, ap t = apparent triplet, m = multiplet, br = broad, br s = broad singlet, br d = broad doublet, dq = doublet of quartets, dt = doublet of triplets, td = triplet of doublets, ap qt = apparent quintet, ap dt = apparent doublet of triplets, number of hydrogens, coupling constant(s) in Hz). Proton-decoupled ^{13}C NMR spectra were recorded on either a Varian Gemini 300 (75 MHz) or Bruker AC 300/P (75 MHz) spectrometers and are recorded in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm or C_6D_6 at 128 ppm), unless otherwise indicated. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a HP-5988-A GC-MS spectrometer. Optical rotations were measured on a Polamat A polarimeter from Carl Zeiss, using a 1 mL quartz cell, with mercury or sodium lamps, and are reported as follows: $[\alpha]_\lambda^t$, (c = g/100 mL, solvent).

Benzylallyl(trimethyl)silane (6)

In a 3-necked 500 mL round bottomed flask was heated powdered $CeCl_3 \cdot 7H_2O$ (15.44 g, 41.4 mmol) under vacuum (1 Torr) at 160 °C for 12 h with vigorous stirring, resulting in the formation of a mobile white solid. The reaction flask was flushed with argon and allowed to cool to r.t. when anhyd THF (65 mL) was added to the vigorously stirred anhyd cerium(III) chloride forming a uniform white suspension, which was kept under stirring for 2 h. During this time, a separate three-necked 100 mL flask, fitted with a condenser and a pressure-equalizing dropping funnel, was charged with Mg turnings (1 g, 41.4 mmol), and the whole apparatus was flame dried

under a flow of argon. To this flask was added dropwise a solution of $ClCH_2SiMe_3$ (5.8 mL, 41.4 mmol) in anhyd THF (27 mL). This mixture was stirred for 3 h until almost all of the Mg had dissolved. The anhyd $CeCl_3$ suspension was now cooled to –78 °C. To this suspension was added dropwise the previously prepared Grignard reagent, forming an off-white suspension, and was stirred at –78 °C for 2 h. At this time, a solution of ester **5** (2.07 g, 13.8 mmol) in anhyd THF (8 mL) was added to the Grignard-cerium chloride complex dropwise over 5 min, and the resulting mixture was warmed gradually to r.t. When consumption of the starting ester was complete, as determined by TLC (3 h), the resulting grey solution was cooled to 0 °C and quenched by the addition of a sat. aq solution of NH_4Cl (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a slightly yellow liquid that was dissolved in CH_2Cl_2 (100 mL). To this flask was added Amberlyst 15 (1.0 g) and this mixture was stirred at r.t. until complete consumption of starting material. The resin was then removed by filtration and washed with CH_2Cl_2 (100 mL). The solvent was removed under reduced pressure to give allylsilane **6** as a colorless liquid; yield: 2.73 g (97%); R_f 0.60 (hexane).

IR (neat): 3065, 3028, 2958, 2916, 1716, 1632, 1064, 1491, 1457, 1416, 1244, 1162, 1073, 1026, 856, 744, 697 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.0 (s, 9 H), 1.44 (s, 2 H), 3.23 (s, 2 H), 4.53 (br s, 1 H), 4.58 (br s, 1 H), 7.10–7.25 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = –1.0, 26.1, 45.1, 109.5, 126.0, 128.2, 129.1, 138.9, 146.7.

MS (70 ev): *m*/*z* (%) = 204 (M^+, 12), 189 (2), 173 (5), 147 (40), 134 (21), 115 (24), 104 (7), 91 (87), 73 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{20}Si$: 204.1334, found: 204.1354.

Anal. Calcd for $C_{13}H_{20}Si$: C, 76.40; H, 9.86; Si, 13.74. Found: C, 76.32; H, 9.81.

Homoallylic Alcohols 14a–c; General Procedure

To a solution of allylsilane **9** (1.5 mmol) in CH_2Cl_2 (5 mL) at r.t. was added $SnCl_4$ (1.4 mmol). The resulting solution was stirred at r.t. for 2 h and then cooled to –78 °C when a solution of aldehyde **13a–c** (1.4 mmol) in CH_2Cl_2 (2 mL) was added. This mixture was stirred for 2 h at –78 °C and quenched by the slow addition of a sat. aq solution of $NaHCO_3$ (5 mL) followed by CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (30% EtOAc–hexane) gave the corresponding homoallylic alcohols **14a–c**.

***tert*-Butyl (1*S*,2*S*)-2-Hydroxy-1-methylpent-4-enylcarbamate (14a)**

Yield: 85%; R_f 0.38 (20% EtOAc–Hexane).

IR (neat): 3422, 2976, 2932, 1684, 1508, 1456, 1391, 1366, 1248, 1169, 1097, 1045, 1027, 990, 914, 865, 781 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (d, 3 H, *J* = 6.9 Hz), 1.44 (s, 9 H), 2.22 (m, 2 H), 2.32 (m, 1 H), 3.55 (m, 1 H), 3.67 (br s, 1 H), 4.74 (br s, 1 H), 5.12 (s, 1 H), 5.13 (s, 1 H), 5.16 (s, 1 H), 5.83 (m, 1 H).

HRMS: *m*/*z* calcd for $C_{11}H_{21}NO_3$: 215.1521; found: 170.0526 (M^+ – 45).

***tert*-Butyl (1*S*,2*S*)-1-Benzyl-2-hydroxypent-4-enylcarbamate (14b)**

Yield: 86%; R_f 0.33 (20% EtOAc–hexane).

IR (neat): 3430, 3064, 3026, 2978, 2931, 2248, 1689, 1641, 1604, 1562, 1496, 1453, 1392, 1366, 1283, 1250, 1169, 1051, 1022, 915, 867, 734, 700, 647, 547 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.41 (s, 9 H), 2.10 (d, 1 H, *J* = 3.7 Hz), 2.25 (d, 2 H, *J* = 6.9 Hz), 2.94 (m, 2 H), 3.60 (br s, 1 H), 3.79 (dd, 1 H, *J* = 8.6, 7.5 Hz), 4.87 (d, 1 H, *J* = 8.6 Hz), 5.10 (s, 1 H), 5.15 (s, 1 H), 5.76 (m, 1 H), 7.25 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.1, 38.6, 39.1, 55.1, 70.0, 79.3, 118.7, 126.5, 128.6, 129.5, 134.0, 138.4, 156.3.

HRMS: *m*/*z* calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 200.0505 (M^+ – 91).

***tert*-Butyl (1*S*,2*S*)-2-Hydroxy-1-isopropylpent-4-enylcarbamate (14c)**

Yield: 85%; R_f 0.38 (20% EtOAc–hexane).

IR (neat): 3422, 2976, 2932, 1684, 1508, 1456, 1391, 1366, 1248, 1169, 1097, 1045, 1027, 990, 914, 865, 781 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, 3 H, *J* = 6.6 Hz), 0.97 (d, 3 H, *J* = 5.5 Hz), 1.45 (s, 9 H), 1.85 (m, 1 H), 1.90 (br d, 1 H), 2.26 (m, 2 H), 3.21 (br t, 1 H, *J* = 8.0 Hz,), 3.82 (br s, 1 H), 4.80 (br s, 1 H), 5.18 (s, 1 H), 5.21 (br s, 1 H), 5.84 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.1, 19.7, 28.3, 30.3, 39.6, 59.3, 69.9, 79.0, 118.5, 134.7, 156.7.

Homoallylic Alcohols 16a–c; General Procedure

To a solution of allylsilane **8** (1.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $SnCl_4$ (1.5 mmol). The resulting solution was stirred at 0 °C for 5 min and then cooled to –78 °C when a solution of aldehyde **13a–c** (1.5 mmol) in CH_2Cl_2 (2 mL) was added. This mixture was stirred for 2 h at –78 °C and quenched by the slow addition of a sat. aq solution of $NaHCO_3$ (5 mL) followed by CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (30% EtOAc–hexane) gave the corresponding homoallylic alcohols **16a–c**.

***tert*-Butyl (1*S*,2*S*)-4-[(1*S*)-2-Benzyloxy-1-methylethyl]-2-hydroxy-1-methylpent-4-enylcarbamte (16a)**

Yield: 88%; $[\alpha]_D^{20}$ +27.48 (*c* = 1.6, $CHCl_3$); R_f 0.30 (20% EtOAc–hexane).

IR (neat): 3442, 3065, 3029, 2963, 2871, 1713, 1643, 1497, 1453, 1390, 1365, 1246, 1171, 1094, 1019, 876, 735, 697 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.01 (d, 3 H, *J* = 6.8 Hz), 1.21 (d, 3 H, *J* = 6.8 Hz), 1.45 (s, 9 H), 2.21 (m, 1 H), 2.49 (m, 2 H), 2.82 (br s, 1 H), 3.37 (dd, 1 H, *J* = 9.0, 5.7 Hz), 3.46 (t, 2 H, *J* = 9.0 Hz), 3.69 (m, 2 H), 4.50 (s, 2 H), 4.97 (s, 2 H), 7.32 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 18.9, 28.3, 38.8, 40.8, 71.4, 73.0, 74.4, 79.5, 112.6, 127.6, 128.3, 137.8, 148.6, 155.9, 199.7.

HRMS: *m*/*z* calcd for $C_{21}H_{33}NO_4$: 363.2409; found: 219.0860 (M^+ – 144).

Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 68.47; H, 8.91; N, 4.0.

***tert*-Butyl (1*S*,2*S*)-1-Benzyl-4-[(1*S*)-2-benzyloxy-1-methylethyl]-2-hydroxypent-4-enylcarbamate (16b)**

Yield: 84%; $[\alpha]_D^{20}$ +10.8 (*c* = 1.18, $CHCl_3$); R_f 0.29 (20% EtOAc–hexane).

IR (neat): 3375, 3091, 3063, 3030, 2963, 2924, 2857, 1949, 1682, 1643, 1604, 1520, 1453, 1393, 1364, 1314, 1253, 1170, 1087, 1002, 891, 735, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (d, 3 H, *J* = 6.9 Hz), 1.40 (s, 9 H), 2.24 (d, 1 H, *J* = 10.2 Hz), 2.32 (dd, 2 H, *J* = 6.9, 5.8 Hz), 2.91 (m, 3 H), 3.35 (dd, 1 H, *J* = 8.8, 5.5 Hz), 3.41 (t, 1 H, *J* = 5.5 Hz), 3.75 (m, 2 H), 4.45 (s, 2 H), 4.94 (m, 3 H), 7.27 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.5, 28.3, 38.5, 39.2, 40.9, 55.4, 67.7, 73.0, 74.6, 112.7, 127.8, 128.5, 137.8, 138.7, 148.7, 155.9, 199.6.

HRMS: *m*/*z* calcd for $C_{27}H_{37}NO_4$: 439.2722; found: 291.6855 (M^+ – 147).

Anal. Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.26; H, 8.45; N, 3.65.

tert-Butyl (1*S*,2*S*)-4-[(1*S*)-2-Benzyloxy-1-methylethyl]-2-hydroxy-1-isopropylpent-4-enylcarbamate (16c)
Yield: 85%; $[\alpha]_D^{20}$ +56.8 (*c* = 1.04, $CHCl_3$); R_f 0.29 (20% EtOAc–hexane).

IR (neat): 3442, 3065, 3029, 2963, 2871, 1713, 1643, 1497, 1453, 1390, 1365, 1246, 1171, 1094, 1019, 876, 735, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (d, 3 H, *J* = 6.6 Hz), 0.95 (d, 3 H, *J* = 6.6 Hz), 1.03 (d, 3 H, *J* = 6.6 Hz), 1.43 (s, 9 H), 1.82 (m, 2 H), 2.19 (d, 2 H, *J* = 7.3 Hz), 2.46 (m, 1 H), 3.19 (t, 1 H, *J* = 8.6 Hz), 3.43 (m, 2 H), 3.97 (m, 1 H), 4.55 (s, 2 H), 4.87 (d, 1 H, *J* = 10.2 Hz), 4.98 (br s, 2 H), 7.30 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.6, 19.5, 19.8, 28.4, 30.9, 38.9, 41.3, 59.6, 67.7, 73.1, 76.7, 78.7, 112.7, 127.7, 128.4, 137.8, 148.9, 156.5 199.6.

HRMS: *m*/*z* calcd for $C_{23}H_{37}NO_4$: 391.2722; found: 301.7508 (M^+ – 90).

Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.52; N, 3.58. Found: C, 70.87; H, 9.65; N, 3.65.

Allyltrichlorostannane (12)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.95 (d, 3 H, *J* = 6.9 Hz), 2.48 (m, 1 H), 3.19 (d, 1 H, *J* = 10.9 Hz), 3.36 (d, 1 H, *J* = 11.3 Hz), 3.53 (dd, 1 H, *J* = 9.8, 6.9 Hz), 3.70 (dd, 1 H, *J* = 9.8, 4.4 Hz), 4.71 (d, 1 H, *J* = 13.2 Hz), 4.77 (d, 1 H, *J* = 5.8 Hz), 5.04 (s, 1 H), 5.18 (s, 1 H), 7.36 (s, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.6, 39.9, 42.6, 73.0, 74.5, 114.6, 144.0, 127.5, 128.3, 128.6, 138.7.

^{119}Sn NMR ($CDCl_3$, 111.92 MHz): δ = –186.87 (tt, J_{Sn-H} = 136.78 Hz, J_{Sn-H} = 78 Hz).

Acetonides 18a–c; General Procedure
To a stirred solution of the corresponding amino alcohols **16a**, **14b**, **16c** (1.4 mmol) in 2,2-dimethoxypropane (2 mL) at r.t. was added *p*-toluenesulfonic acid (2 mg), and the mixture was stirred for 46 h at r.t. Et_2O (2 mL) was added, and the organic layer was washed with 10% $NaHCO_3$ (1 mL) and brine (1 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10% EtOAc–hexane) afforded products **18a–c**.

tert-Butyl (4*R*,5*R*)-5-{2-[(1*R*)-2-Benzyloxy-1-methylethyl]allyl}-2,2,4-trimethyl-1,3-oxazolane-3-carboxylate (18a)
Yield: 85%; R_f 0.29 (20% EtOAc–hexane).

IR (neat): 3413, 3068, 2980, 2934, 1874, 1699, 1453, 1387, 1258, 1097 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (s, 3 H), 0.88 (d, 3 H, *J* = 6.6 Hz), 1.18 (d, 3 H, *J* = 6.8 Hz), 1.48 (s, 9 H), 2.38 (dd, 1 H, *J* = 7.6, 6.8 Hz), 2.48 (dd, 1 H, *J* = 6.8, 6.1 Hz), 2.56 (dd, 1 H, *J* = 7.6, 6.8 Hz), 3.25 (dd, 1 H, *J* = 7.6, 6.1 Hz), 3.51 (m, 1 H), 4.06 (m, 1 H), 4.58 (d, 2 H, *J* = 6.6 Hz), 4.92 (br s, 1 H), 5.02 (s, 1 H), 7.34 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.5, 28.4, 38.8, 59.5, 67.6, 73.0, 78.7, 112.6, 127.7, 137.8, 148.8, 153.5.

HRMS: *m*/*z* calcd for $C_{24}H_{37}NO_4$: 403.2722; found: 388.1632 (M^+ – 15).

tert-Butyl (4*S*,5*S*)-5-Allyl-4-benzyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (18b)
Yield: 84%; R_f 0.29 (20% EtOAc–hexane).

IR (neat): 3426, 3068, 2974, 2930, 1699, 1460, 1387, 1253, 1175, 708 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.25 (br s, 3 H), 1.53 (s, 12 H), 2.19 (m, 2 H), 2.85 (m, 1 H), 3.23 (dd, 1 H, *J* = 12.8, 2.9 Hz), 3.80 (br s, 1 H), 3.96 (dt, 2 H, *J* = 4.4, 1.8 Hz), 4.9 (br d, 2 H, *J* = 9.1 Hz), 5.50 (br s, 1 H), 7.24 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.9, 28.5, 37.5, 38.0, 62.6, 79.9, 117.4, 126.4, 128.4, 129.4, 129.8, 133.7, 137.7, 151.8.

HRMS: *m*/*z* calcd for $C_{20}H_{29}NO_3$: 331.2147; found: 331.2142.

tert-Butyl (4*R*,5*R*)-5-{2-[(1*R*)-2-Benzyloxy-1-methylethyl]allyl}-4-isopropyl-2,2-dimethyl-1,3-oxazolane-3-carboxylate (18c)
Yield: 80%; R_f 0.29 (20% EtOAc–hexane).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (br s, 3 H), 0.95 (br s, 3 H), 1.11 (d, 3 H, *J* = 6.8 Hz), 1.48 (s, 9 H), 1.78 (m, 1 H), 1.95 (m, 1 H), 2.38 (dd, 1 H, *J* = 7.8, 6.5 Hz), 2.48 (dd, 1 H, *J* = 6.8, 6.1 Hz), 2.56 (dd, 1 H, *J* = 7.6, 6.8 Hz), 3.25 (dd, 1 H, *J* = 7.5, 6.1 Hz), 3.51 (m, 2 H), 4.06 (m, 2 H), 4.58 (d, 2 H, *J* = 6.6 Hz), 4.92 (br s, 2 H), 5.02 (s, 1 H), 7.34 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.0, 22.6, 28.5, 39.6, 51.9, 73.0, 74.6, 80.1, 111.5, 127.4, 128.3, 138.5, 148.1, 152.1.

(4*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenylhex-1-en-4-ol (23)
To a solution of allylsilane **6** (2.86 g, 14 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added $SnCl_4$ (1.7 mL, 14 mmol). The resulting solution was stirred at 0 °C for 2 h and then cooled to –78 °C when a solution of aldehyde **13b** (2.7 g, 11 mmol) in CH_2Cl_2 (20 mL) was added. This mixture was stirred for 2 h at –78 °C and quenched by the slow addition of a sat. aq solution of $NaHCO_3$ (50 mL) followed by CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (30% EtOAc–hexane) gave the corresponding homoallylic alcohol **23** as a white solid.

Yield: 3.95 g (94%); R_f 0.35 (20% EtOAc–hexane); mp 95.5–97.8 °C; $[\alpha]_D^{20}$ –15.0 (*c* = 2.84, CH_2Cl_2).

IR (neat): 3422, 3351, 3066, 3030, 2977, 2929, 1685, 1644, 1507, 1455, 1365, 1252, 1170, 1015, 967, 868, 743, 701, 530 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.39 (s, 9 H), 1.98 (br s, 1 H), 2.08–2.15 (m, 2 H), 2.82–2.93 (m, 2 H), 3.23 (br s, 2 H), 3.65–3.70 (m, 2 H), 4.83 (m, 1 H), 4.88 (br s, 2 H), 7.02 (d, 2 H, *J* = 7.0 Hz), 7.16–7.31 (m, 8 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.4, 38.9, 40.9, 42.8, 55.2, 68.1, 79.2, 114.7, 126.1, 128.3, 128.7, 128.8, 129.2, 138.3, 138.7, 145.1, 155.7.

MS (70 eV): *m*/*z* (%) = 290 (M^+ – 91, 20), 234 (16), 190 (26), 164 (31), 120 (45), 91 (41), 57 (100).

HRMS: *m*/*z* calcd for $C_{24}H_{31}NO_3$: 381.2304, found: 290.1804 (M^+ – 91).

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.30; H, 8.20; N, 3.63.

(2*S*,3*S*)-2-Amino-5-benzyl-1-phenylhex-5-en-3-ol (24)
After stirring at –78 °C for 2 h, the above reaction was allowed to warm to r.t. before it was quenched by the addition of an aq sat. solution of NH_4Cl. This procedure led to the isolation of amino alcohol **24** in 82% yield from α-amino aldehyde **13b**.

Yield: 2.52 g (82%); R_f 0.24 (50% EtOAc–hexane) .

IR (KBr): 3383, 3063, 3030, 2952, 2912, 1945, 1878, 1799, 1632, 1605, 1497, 1453, 1364, 1252, 1061, 894, 843, 742, 704 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.93–1.20 (m, 3 H), 2.05 (dd, 1 H, *J* = 13.8, 6.1 Hz), 2.27 (dd, 1 H, *J* = 13.8, 7.5 Hz), 2.41 (dd, 1 H, *J* = 13.4, 9.2 Hz), 2.64 (dd, 1 H, *J* = 13.4, 5.0 Hz), 2.82 (ddd, 1 H, *J* = 9.1, 5.3, 2.9 Hz), 3.17 (d, 1 H, *J* = 15.0 Hz), 3.24 (d, 1 H, *J* = 15.0 Hz), 3.64 (ddd, 1 H, *J* = 7.4, 6.3, 2.7 Hz), 4.78 (s, 1 H), 4.83 (s, 1 H), 7.03 (d, 2 H, *J* = 7.0 Hz), 7.10–7.30 (m, 8 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 40.1, 41.4, 43.2, 55.4, 73.0, 114.5, 126.0, 126.1, 128.2, 128.3, 128.9, 129.1, 139.0, 139.8, 145.3.

(4*S*,5*S*)-4-Benzyl-5-(2-benzylprop-3-enyl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine (25)
To a stirred solution of the amino alcohol **23** (0.53 g, 1.4 mmol) in 2,2-dimethoxypropane (20 mL) at r.t. was added *p*-toluenesulfonic acid (13 mg), and the mixture was stirred for 46 h at r.t. Et_2O (20 mL) was added and the organic layer was washed with 10% aq $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10% EtOAc–hexane) gave product **25** as a colorless oil.

Yield: 0.54 g (91%); R_f 0.51 (30% EtOAc–hexane); $[\alpha]_D^{20}$ –6.4 (*c* = 1.33, $CHCl_3$).

IR (neat): 3066, 3028, 2972, 2924, 2856, 1945, 1876, 1808, 1702, 1645, 1604, 1491, 1453, 1385, 1256, 1175, 1076, 1032, 896, 741, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 1.50 (br s, 3 H), 1.64 (s, 9 H), 1.69 (s, 3 H), 2.06 (dd, 1 H, *J* = 14.3, 5.9 Hz), 2.22 (dd, 1 H, *J* = 14.3, 7.3 Hz), 2.84–2.92 (m, 1 H), 3.22 (br s, 2 H), 3.30 (dd, 1 H, *J* = 12.9, 3.1 Hz), 3.91–3.97 (m, 1 H), 4.18 (ddd, 1 H, *J* = 7.3, 5.9, 4.0 Hz), 4.80 (s, 2 H), 7.11 (d, 2 H, *J* = 6.6 Hz), 7.25–7.39 (m, 8 H).

^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 27.2, 28.4, 28.6, 35.1, 40.9, 42.8, 63.3, 77.8, 80.0, 94.3, 114.2, 126.2, 126.6, 128.4, 128.6, 129.1, 129.8, 138.2, 139.5, 145.3, 152.3.

HRMS: *m*/*z* calcd for $C_{27}H_{35}NO_3$: 421.2617, found: 421.1827.

Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 77.28; H, 8.17; N, 3.45.

(4*S*,5*S*)-4-Benzyl-5-(2-benzylprop-2-enyl)-1,3-oxazolidin-2-one (26)
To a solution of amino alcohol **24** (60 mg, 0.213 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added slowly a solution of triphosgene (76 mg, 0.256 mmol) in CH_2Cl_2 (1.2 mL). The mixture was stirred for 3 h at r.t., diluted with CH_2Cl_2 (10 mL), and washed with aq sat. $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the organic layer dried ($MgSO_4$) and concentrated to provide the crude product, which was purified by flash chromatography (20% EtOAc–hexane).

Yield: 46 mg (70%); R_f 0.52 (50% EtOAc–hexane).

IR (film): 3278, 3068, 3028, 2917, 2852, 1754, 1644, 1600, 1494, 1456, 1389, 1246, 1096, 1013, 902, 735, 703 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.10 (dd, 1 H, *J* = 14.6, 6.0 Hz), 2.33 (dd, 1 H, *J* = 14.6, 7.3 Hz), 2.72 (dd, 1 H, *J* = 13.4, 6.3 Hz), 2.81 (dd, 1 H, *J* = 13.4, 7.0 Hz), 3.20 (d, 1 H, *J* = 15.4 Hz), 3.26 (d, 1 H, *J* = 15.4 Hz), 3.63 (q, 1 H, *J* = 6.0 Hz), 4.37 (q, 1 H, *J* = 6.0 Hz), 4.86 (s, 1 H), 4.89 (s, 1 H), 5.98 (br s, 1 H), 7.08–7.33 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 40.1, 41.4, 43.0, 58.5, 79.9, 115.4, 126.3, 127.1, 128.3, 128.8, 128.9, 135.7, 138.5, 142.9, 158.5.

Hydroboration of Acetonide 25
To a solution of acetonide **25** (0.59 g, 1.4 mmol) in THF (10 mL) cooled to 0 °C was added the $BH_3{\cdot}SMe_2$ complex (0.9 mL of a 2 M solution in THF, 1.8 mmol). This mixture was stirred at 0 °C until complete consumption of starting material, as determined by TLC (ca. 24 h). EtOH (2 mL) was added followed by an aq 3 M solution of NaOH (6 mL) and 30% H_2O_2 (6 mL). The mixture was stirred 10 h at r.t. EtOAc (10 mL) was added, and the organic layer was separated and washed with aq 10% Na_2SO_3 (10 mL) and brine (10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (30% Et_2O–hexane) produced the desired product (2′*R*,4*S*,5*S*)-**27** (0.34 g, 55%) and its isomer (2′*S*,4*S*,5*S*)-**28** (0.23 g, 38%) as colorless oils.

(4*S*,5*S*)-4-Benzyl-5-[(2*R*)- 2-benzyl-3-hydroxypropyl]-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine (27)
Yield: 0.32 g (55%); $[\alpha]_D^{20}$ +4.1 (*c* = 2.44, $CHCl_3$); R_f 0.35 (70% Et_2O–hexane).

IR (neat): 3452, 3027, 2978, 2931, 1696, 1496, 1455, 1392, 1367, 1255, 1174, 1075 cm^{-1}.

^1H NMR (C_6D_6, 300 MHz, 65 °C): δ = 1.38 (m, 6 H), 1.45 (s, 9 H), 1.67 (br s, 3 H), 1.73–1.78 (m, 1 H), 2.38 (dd, 1 H, *J* = 12.9, 6.8 Hz), 2,47 (dd, 1 H, *J* = 12.9, 7.3 Hz), 2.72–2.92 (m, 1 H), 3.19–3.35 (m, 3 H), 3.68–3.79 (m, 1 H), 3.99 (ddd, 1 H, *J* = 9.2, 5.4, 3.8 Hz), 6.97–7.13 (m, 10 H).

^1H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 1.25–1.33 (m, 2 H), 1.45 (br s, 3 H), 1.52 (s, 9 H), 1.57 (br s, 3 H), 1.70–1.73 (m, 1 H), 1.83–2.14 (m, 1 H), 2.40 (dd, 1 H, *J* = 13.7, 6.8 Hz), 2.51 (dd, 1 H, *J* = 13.7, 7.3 Hz), 2.75–2.91 (m, 1 H), 3.15 (dd, 1 H, *J* = 13.1, 3.3 Hz), 3.34–3.38 (m, 1 H), 3.42–3.47 (m, 1 H), 3.54–3.75 (m, 1 H), 3.92 (ddd, 1 H, *J* = 8.9, 5.3, 3.7 Hz), 7.02 (br d, 2 H, *J* = 6.6 Hz), 7.08 (d, 2 H, *J* = 7.2 Hz), 7.18–7.25 (m, 6 H).

^{13}C NMR (C_6D_6, 75 MHz, 65 °C): δ = 27.3, 28.7, 28.8, 30.8, 37.2, 38.3, 41.0, 64.7, 65.3, 78.3, 79.7, 94.6, 126.1, 126.7, 128.5, 128.7, 129.5, 130.0, 138.4, 140.8, 152.1.

^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 26.7, 28.4, 28.5, 29.6, 36.8, 38.1, 40.8, 63.9, 65.3, 77.9, 80.0, 94.4, 125.9, 126.7, 128.3, 128.4, 129.1, 129.7, 137.7, 140.2, 152.0.

HRMS: *m*/*z* calcd for $C_{27}H_{37}NO_4$: 439.2723, found: 324.1949 ($M^+ - 105$).

Anal. Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19: Found: C, 73.70; H, 8.41; N, 3.17.

(4*S*,5*S*)-4-Benzyl-5-[(2*S*)-2-benzyl-3-hydroxypropyl]-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine (28)
Yield: 0.23 g (38%); $[\alpha]_D^{20}$ +5.3 (*c* = 1.89, $CHCl_3$); R_f 0.40 (70% Et_2O–hexane).

IR (film): 3469, 3062, 3027, 2979, 2933, 1695, 1604, 1496, 1478, 1455, 1392, 1367, 1256, 1208, 1174, 1077, 1031, 868, 770, 740, 701, 516 cm^{-1}.

^1H NMR (C_6D_6, 300 MHz, 65 °C): δ = 1.35 (br s, 2 H), 1.46–1.49 (m, 1 H), 1.53 (br s, 12 H), 1.82–1.88 (m, 2 H), 2.42 (dd, 1 H, *J* = 13.6, 6.8 Hz), 2.58 (dd, 1 H, *J* = 13.6, 7.9 Hz), 2.77–2.84 (m, 1 H), 3.20 (dd, 1 H, *J* = 13.2, 2.9 Hz), 3.39 (dd, 1 H, *J* = 10.8, 5.1 Hz), 3.46 (dd, 1 H, *J* = 10.8, 4.4 Hz), 3.73–3.79 (m, 1 H), 4.07 (ap dt, 1 H, *J* = 13.0, 4.2 Hz), 7.02 (d, 2 H, *J* = 7.0 Hz), 7.15–7.31 (m, 8 H).

^{1}H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 1.35 (br s, 4 H), 1.46–1.49 (m, 1 H), 1.53 (s, 12 H), 1.82–1.88 (m, 1 H), 2.42 (dd, 1 H, *J* = 13.7, 6.8 Hz), 2.58 (dd, 1 H, *J* = 13.7, 7.9 Hz), 2.77–2.84 (m, 1 H), 3.21 (dd, 1 H, *J* = 13.2, 2.9 Hz), 3.39 (dd, 1 H, *J* = 11.0, 5.1 Hz), 3.46 (dd, 1 H, *J* = 11.0, 4.6 Hz), 3.73–3.82 (m, 1 H), 4.07 (ap dt, 1 H, *J* = 8.8, 4.4 Hz), 7.02 (br d, 2 H, *J* = 7.0 Hz), 7.17–7.27 (m, 8 H).

^{13}C NMR (C_6D_6, 75 MHz, 65 °C): δ = 27.3, 28.5, 28.8, 30.1, 36.2, 38.3, 40.0, 64.3, 64.5, 77.4, 79.7, 94.6, 126.1, 126.7, 128.5, 128.7, 129.5, 130.1, 138.5, 140.8, 152.1.

^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 26.9, 28.1, 28.6, 29.7, 36.6, 37.7, 39.4, 63.7, 64.4, 77.2, 80.0, 94.3, 125.9, 126.6, 128.3, 128.5, 129.1, 129.7, 137.9, 140.3, 152.1.

HRMS: *m*/*z* calcd for $C_{27}H_{37}NO_4$: 439.2723, found: 324.1955 ($M^+ - 105$).

Anal. Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.69; H, 8.42; N, 3.16.

(2*S*,3*S*,5*S*)-2,5-Dibenzylpiperidin-3-ol (29)

To a solution of imidazole (34.4 mg, 0.51 mmol) and Ph_3P (48.6 mg, 0.185 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added I_2 (47 mg, 0.19 mmol). This mixture was stirred at 0 °C for 15 min and then a solution of the alcohol (2′*S*,4*S*,5*S*)-**28** (74 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added. The resulting mixture was stirred at 0 °C for 15 min and then at r.t. for 12 h. The mixture was diluted with a sat. aq solution of $Na_2S_2O_3$ (1 mL) followed by addition of H_2O (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated to provide the crude product, which was purified by flash chromatography (5% EtOAc–hexane) to give 63 mg (68%) of the intermediate iodide. To a solution of this iodide (63 mg, 0.115 mmol) in a 50:50 mixture of EtOAc–DMF (2 mL) was added aq 4 M HCl (1.8 mL). This mixture was stirred at r.t. for 3 h, quenched by the addition of K_2CO_3 (0.5 g) and H_2O (5 mL) and allowed to stir at r.t. for 2 h. The volatiles were removed under reduced pressure and the remaining solvent was removed in vacuo (2 Torr). The product was purified by flash cromatography (5% MeOH–CH_2Cl_2).

Yield: 30 mg (63%); R_f 0.29 (70% MeOH–CH_2Cl_2).

IR (film): 3470, 3061, 3025, 2960, 2930, 1497, 1475, 1450, 1390, 1365, 1252, 1206, 1170, 1030, 865, 770 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.76 (ddd, 1 H, *J* = 12.7, 7.4, 5.5 Hz), 1.87 (dt, 1 H, *J* = 12.2, 7.6 Hz), 1.92 (br s, 2 H), 2.49 (dd, 1 H, *J* = 13.4, 9.5 Hz), 2.57 (m, 1 H), 2.69 (d, 2 H, *J* = 7.6 Hz), 2.80 (dd, 1 H, *J* = 13.4, 4.0 Hz), 2.89 (m, 1 H), 3.49 (dd, 1 H, *J* = 8.54, 6.1 Hz), 3.89 (q, 1 H, *J* = 6.7 Hz), 3.92 (dd, 1 H, *J* = 8.4, 6.3 Hz), 7.16–7.30 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 34.6, 39.3, 40.8, 41.2, 56.8, 73.0, 81.8, 125.9, 126.1, 128.3, 128.4, 128.6, 129.1, 138.8, 140.4.

HRMS: *m*/*z* calcd for $C_{19}H_{23}NO_4$: 281.1780, found: 281.1824.

Lactones 32 and 33

To a solution of amino alcohol **23** (2.25 g, 5.90 mmol) in THF (70 mL) cooled to 0 °C was added the $BH_3{\cdot}SMe_2$ complex (15.8 mL of a 2 M solution in THF, 29.5 mmol). This mixture was stirred at 0 °C until complete consumption of starting material, as determined by TLC (ca.24 h). EtOH (36 mL) was added followed by an aq 3 M solution of NaOH (74 mL) plus 30% H_2O_2 (56 mL). The mixture was stirred at r.t. for 10 h. EtOAc (20 mL) was added and the organic layer was separated and washed with aq 10% Na_2SO_3 (20 mL) and brine (20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (50% EtOAc–hexane) gave a mixture of diols **30** and **31** (2.19 g, 93% yield) as a colorless oil. Solid TPAP (192 mg, 0.59 mmol) was added in one portion to a stirred mixture of diols **30** and **31** (2.18 g, 5.60 mmol), then a mixture of NMO (1.92 g, 16.5 mmol) and activated powdered molecular sieves (2.74 g) in CH_2Cl_2 (6 mL) was added at r.t. under argon. On completion of the reaction, the mixture was filtered through a pad of silica gel, eluting with 7% EtOAc–hexane. The filtrate was evaporated and the residue was purified by column chromatography on silica gel using 7% EtOAc–hexane to give lactones **32** and **33**, respectively, in 95% overall yield.

(3*R*,5*S*)-3-Benzyl-5-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}dihydrofuran-2-(3*H*)-one (32)

Yield: 1.15 g (53%); R_f 0.60 (30% EtOAc–hexane).

IR (film): 3340, 3027, 2975, 2927, 2848, 1769, 1706, 1493, 1457, 1367, 1245, 1166, 1028, 965, 747, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (s, 9 H), 1.96 (m, 1 H), 2.22 (m, 1 H), 2.76 (dd, 1 H, *J* = 13.5, 8.8 Hz), 2.85 (m, 2 H), 2.97 (m, 1 H), 3.10 (dd, 1 H, *J* = 13.5, 4.4 Hz), 3.93 (br q, 1 H, *J* = 8.4 Hz), 4.20 (m, 1 H), 4.57 (br d, 1 H, *J* = 9.5 Hz), 7.20 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.3, 29.4, 36.9, 39.1, 41.4, 54.5, 78.3, 79.9, 126.5, 126.7, 128.4, 128.5, 128.7, 129.1, 136.9, 137.7, 155.6, 178.9.

(3*S*,5*S*)-3-Benzyl-5-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}dihydrofuran-2-(3*H*)-one (33)

Yield: 0.911 g (42%); R_f 0.56 (30% EtOAc–hexane).

IR (film): 3347, 3065, 3030, 2978, 2927, 2855, 1774, 1703, 1602, 1497, 1451, 1365, 1247, 1170, 1042, 740, 705 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (s, 9 H), 1.79 (br q, 1 H, *J* = 12.0 Hz), 2.06 (m, 1 H), 2.68 (dd, 1 H, *J* = 13.7, 10.0 Hz), 2.81–3.0 (m, 3 H), 3.25 (dd, 1 H, *J* = 13.5, 3.7 Hz), 3.93 (br q, 1 H, *J* = 8.4 Hz), 4.3 (dd, 1 H, *J* = 9.2, 6.2 Hz), 4.61 (br d, 1 H, *J* = 10.0 Hz), 7.11–7.30 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.3, 30.5, 36.2, 39.4, 42.6, 53.2, 77.7, 79.8, 126.6, 128.5, 128.8, 129.2, 137.0, 138.2, 155.7, 177.7.

(2*R*,4*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-1-indanyl]-6-phenylhexanamide (1)

A solution of **32** (982 mg, 2.4 mmol) in 1,4-dioxane (14 mL) was treated with a solution of LiOH in H_2O (1 M, 2.6 mL, 2.6 mmol) and stirred at r.t. for 3 h. The reaction mixture was carefully acidified to pH 4 with citric acid and then extracted with EtOAc. The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude hydroxy acid was dissolved in DMF (30 mL), treated with *tert*-butyldimethylsilyl chloride (3.63 g, 24 mmol) and imidazole (1.95 g, 28.6 mol), and stirred for 24 h. MeOH (20 mL) was added to the mixture and it was stirred for 3 h, evaporated in vacuo, and then partitioned between 10% aq citric acid (50 mL) and EtOAc (200 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. Purification by flash column chromatography (3% MeOH–CH_2Cl_2) gave **19** (1.19 g, 94%) as a white foam. A solution of **19** (100 mg, 0.188 mmol), (1*S*,2*R*)-1-amino-2-hydroxyindan (**34**; 34.7 mg, 0.23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (51 mg, 0.27 mmol) and 1-hydroxybenzotriazole (31 mg, 0.26 mmol) in DMF (5 mL) was stirred at r.t. for 15 h. The reaction mixture was diluted with EtOAc (25 mL) and the organic phase was washed with aq citric acid (pH 4), aq $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash column chromatography (20% EtOAc–hexane) gave the corresponding silylated product.

Yield: 100 mg (80%); R_f 0.32 (30% EtOAc–hexane).

Silylated Product

IR (film): 3322, 2957, 2856, 2796, 1710, 1655, 1500, 1462, 1362, 1251, 1173, 1091, 841, 780, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.11 (s, 3 H), 0.15 (s, 3 H), 0.96 (s, 9 H), 1.26 (s, 9 H), 1.75–1.79 (m, 2 H), 1.96–2.01 (m, 2 H), 2.56–2.62 (m, 2 H), 2.76–2.84 (m, 4 H), 3.0 (dd, 1 H, *J* = 16.6, 5.0 Hz), 3.85 (br dd, 1 H, *J* = 8.5, 4.0 Hz), 3.99 (br q, 1 H, *J* = 8.8 Hz), 4.23 (br t, 1 H, *J* = 4.9 Hz), 4.83 (d, 1 H, *J* = 9.5 Hz), 5.25 (dd, 1 H, *J* = 8.7, 4.8 Hz), 5.96 (d, 1 H, *J* = 8.8 Hz), 7.12–7.32 (m, 14 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = –4.4, –3.9, 18.1, 25.9, 28.2, 37.3, 38.4, 38.9, 39.1, 46.7, 54.1, 57.4, 70.7, 73.1, 79.5, 124.2, 124.9, 126.4, 126.5, 126.7, 127.8, 128.5, 128.6, 129.0, 129.1, 138.5, 139.8, 140.1, 140.2, 156.0, 174.5.

This material was dissolved in a solution of Bu_4NF in THF (1 M, 1.25 mL) and stirred at r.t. for 12 h. The reaction mixture was diluted with citric acid in Et_2O (pH 4) and the resulting precipitate was collected by filtration, washed and dried in vacuo. Further purification by flash column chromatography (6% MeOH/CH_2Cl_2) gave L-685-434 (**1**) as a white solid.

L-685,434 (1)

Yield: 90 mg (88%); R_f 0.21 (60% EtOAc–hexane); $[\alpha]_D^{25}$ +16.7 (*c* = 0.28, MeOH); mp 194.3–197.5 °C.

IR (KBr) 3447, 3365, 3061, 3022, 2917, 2849, 1665, 1645, 1537, 1392, 1278, 1158, 1058, 899, 862, 733, 703, 649 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.37 (s, 9 H), 1.80–1.96 (m, 2 H), 2.72–2.95 (m, 6 H), 3.02 (dd, 1 H, *J* = 16.8, 5.1 Hz), 3.45 (m, 1 H), 3.68 (m, 1 H), 3.81 (m, 1 H), 4.22 (t, 1 H, *J* = 4.8 Hz), 4.81 (d, 1 H, *J* = 9.5 Hz), 5.23 (dd, 1 H, *J* = 8.4, 5.1 Hz), 5.87 (d, 1 H, *J* = 8.4 Hz), 7.05 (br s, 1 H), 7.05–7.30 (m, 14 H).

^{13}C NMR (DMSO-d_6, 125 MHz,): δ = 28.5, 37.5, 39.0, 39.1, 39.6, 47.1, 57.4, 57.6, 69.3, 73.1, 79.6, 124.1, 125.1, 126.4, 126.5, 127.0, 128.0, 128.4, 128.5, 129.0, 129.3, 138.4, 139.8, 140.1, 140.3, 156.2, 175.4.

HRMS: *m*/*z* calcd for $C_{33}H_{40}N_2O_5$: 544.2937, found: 544.2888.

(1*R*)-3-Benzyl-1-{(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl}but-3-enyl 4-Nitrobenzoate (37)

Method A: To a stirred solution of alcohol **23** (1.14 g, 3 mmol), Ph_3P (6.2 g, 24 mmol) and *p*-nitrobenzoic acid (3.9 g, 24 mmol) in THF (50 mL) at r.t. was added di-*tert*-butyl azodicarboxylate (5.4 g) in THF (10 mL). The solution was then stirred at r.t. for 18 h, whereupon the volatile components were removed in vacuo and the residue purified by flash chromatography on silica gel (15% EtOAc–hexane) to give **37** as a white crystalline solid and **38** as a colorless oil.

Yield: 955 mg (60%); R_f 0.47 (30% EtOAc–hexane); mp 137.1–138.8 °C; $[\alpha]_D^{25}$ +10.0 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3375, 3065, 3032, 2984, 2926, 2852, 1953, 1715, 1691, 1609,1520, 1454, 1331, 1265, 1176, 1127, 995, 874, 742, 717 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.24 (s, 9 H), 2.37 (m, 2 H), 2.62 (br d, 1 H, *J* = 13.8, 9.2 Hz), 2.84 (dd, 1 H, *J* = 13.8, 4.9 Hz), 3.29 (d, 1 H, *J* = 15.2 Hz), 3.36 (d, 1 H, *J* = 15.2 Hz), 4.14–4.28 (m, 1 H), 4.44 (d, 1 H, *J* = 9.2 Hz), 4.74 (br s, 1 H), 4.84 (br s, 1 H), 5.34–5.37 (m, 1 H), 7.07–7.22 (m, 10 H), 8.05 (d, 2 H, *J* = 8.6 Hz), 8.19 (d, 2 H, *J* = 8.6 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.1, 36.5, 36.6, 42.4, 53.3, 75.0, 79.6, 115.3, 123.5, 126.4, 126.7, 128.5, 128.6, 129.1, 130.8, 135.7, 137.2, 138.9, 144.1, 150.6, 155.3, 164.2.

MS: *m*/*z* (%) = 530 (M^+, 55), 225 (67), 91 (32), 57 (100).

HRMS: *m*/*z* calcd for $C_{31}H_{34}N_2O_6$: 530.2417; found: 530.9723.

***tert*-Butyl (1*S*,2*E*)-1,4-Dibenzylpenta-2,4-dienylcarbamate (38)**

Yield: 109 mg (10%); R_f 0.64 (20% EtOAc–hexane).

IR (film): 3415, 3351, 3060, 3031, 2974, 2928, 2854, 1945, 1882, 1704, 1602, 1487, 1453, 1367, 1253, 1167, 1018, 967, 893, 802, 732, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.42 (s, 9 H), 2.78 (br s, 2 H), 3.52 (s, 2 H), 4.35–4.50 (m, 2 H), 4.92 (s, 1 H), 5.12 (s, 1 H), 5.60 (ap dt, 1 H, *J* = 15.8, 2.7 Hz), 6.14 (d, 1 H, *J* = 15.8 Hz), 6,96 (br d, 2 H, *J* = 7.7 Hz), 7.14–7.34 (m, 8 H).

(4*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenylhex-1-en-4-ol (39)

To a solution of ester **37** (557 mg, 1.05 mmol) in a mixture of EtOH–H_2O–THF (75 mL, 2:1:2) was added LiOH (150 mg, 0.60 mmol). After 1 h, the reaction mixture had turned yellow and to it was added Et_2O (75 mL) and sat. aq NH_4Cl (75 mL). After separation, the organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by recrystallization (5% EtOAc–hexane) to give 392 mg of **39** as a white solid in 98% yield.

Method B: To a stirred solution of alcohol **23** (103 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon was added Dess–Martin periodinane (229 mg, 0.54 mmol) and the stirring was continued for 1 h. Sat. aq $NaHCO_3$ (5 mL), aq $Na_2S_2O_3$ (1.5 M, 4 mL) and Et_2O were added and stirring was continued for 15 min at r.t. The aqueous layer was further extracted with Et_2O and the combined organic layers were dried, filtered and concentrated. To a solution of the crude ketone **40** in THF (3 mL) at 0 °C was added dropwise a 1 M solution of $LiBH_4$ in THF (0.5 mL, 0.5 mmol). After 24 h, the solution was quenched with H_2O (2 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by recrystallization (5% EtOAc–hexane) to give **39** (62.8 mg) as a white solid.

Yield: 61% overall; mp 141.5–142.3 °C; R_f 0.32 (30% EtOAc–hexane).

IR (KBr): 3365, 3065, 3028, 2928, 2852, 1685, 1644, 1528, 1450, 1369, 1316, 1269, 1169, 1073, 1015, 909, 873, 732, 697, 644, 537 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (br s, 9 H), 2.16 (dd, 2 H, *J* = 14.3, 9.2 Hz), 2,29 (m, 1 H), 2,77 (m, 1 H), 2.89 (dd, 1 H, *J* = 14.3, 4.0 Hz), 3.36 (d, 1 H, *J* = 15.0 Hz), 3.42 (d, 1 H, *J* = 15.0 Hz), 3.80 (m, 2 H), 4.56 (br d, 1 H, *J* = 7.7 Hz), 4.95 (br s, 1 H), 5.00 (br s, 1 H), 7.15–7.34 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.2, 35.5, 39.9, 42.8, 56.1, 71.1, 79.5, 114.8, 126.3, 128.3, 128.4, 128.6, 129.0, 129.4, 135.7, 138.1, 145.6, 156.0.

MS: *m*/*z* (%) = 290 (M^+ – 91, 11), 216 (7), 190 (16), 164 (45), 120 (74), 91 (46), 57 (100).

HRMS: *m*/*z* calcd for $C_{24}H_{31}NO_3$: 381.2304; found: 290.0425 (M^+ – 91).

Anal. Calcd for $C_{24}H_{31}NO_3$: C 75.56, H 8.19, N 3.67; found: C 75.41, H 8.13, N 3.62.

(4*S*,5*R*)-4-Benzyl-5-(2-benzylprop-3-enyl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine (41)

To a stirred solution of the amino alcohol **39** (76 mg, 0.2 mmol) in 2,2-dimethoxypropane (1 mL) at r.t., was added *p*-toluenesulfonic acid (1.5 mg), and the mixture was stirred for 46 h at r.t. Et_2O (5 mL) was added, and the organic layer was washed with 10% $NaHCO_3$ (3 mL) and a sat. aq solution of NaCl (2 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10% EtOAc–hexane) gave product **41** as a colorless oil.

Yield: 65 mg (77%); R_f 0.56 (20% EtOAc–hexane); $[\alpha]_D^{20}$ +5.6 (*c* = 1.8, $CHCl_3$).

IR (neat): 3440, 3063, 3027, 2979, 2933, 1696, 1647, 1604, 1496, 1455, 1386, 1355, 1251, 1087, 1029 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 1.34 (br s, 9 H), 1.51 (s, 3 H), 1.58 (s, 3 H), 2.02 (dd, 1 H, *J* = 15.9, 4.0 Hz), 2.29 (dd, 1 H, *J* = 15.9, 8.2 Hz), 2.78 (br d, 1 H, *J* = 6.6 Hz), 3.28 (s, 2 H), 4.03–4.16 (m, 1 H), 4.21 (ddd, 1 H, *J* = 8.2, 4.8, 4.0 Hz), 4.79 (s, 1 H), 4.84 (s, 1 H), 7.09–7.26 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 24.1, 37.8, 28.5, 35.2, 36.5, 44.0, 60.8, 75.8, 79.6, 92.7, 112.5, 125.9, 126.1, 127.0, 128.2, 129.0, 129.4, 139.0, 139.3, 145.5, 151.8.

HRMS: *m*/*z* Calcd for $C_{27}H_{35}NO_3$: 421.2617, found: 330.2040 ($M^+ - 91$).

Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 77.02; H, 8.21; N, 3.35.

tert-Butyl (1*S*)-2-Amino-1-benzyl-2-oxoethylcarbamate

A solution of *N*-Boc-Phe **36** (1.35 g, 5.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.06 g, 5.61 mmol) and 1-hydroxybenzotriazole (669 mg, 5.61 mmol) in a mixture of DMF (10 mL) and CH_2Cl_2 (20 mL) was stirred at r.t. for 1 h. To the resulting suspension was aq (0.78 mL, 10.2 mmol) at 0 °C and the mixture was stirred for 2 h at 0 °C and 18 h at r.t. The mixture was diluted with EtOAc (25 mL) and the organic phase was washed with aq citric acid (pH 4), aq $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo.

Boc-Protected 22

Yield: 1.12 g (90%); mp 148.2–151.5 °C; R_f 0.34 (60% EtOAc–hexane); $[\alpha]_D^{20}$ +12.3 (*c* = 0.82, MeOH).

IR (KBr): 3390, 3347, 3194, 2986, 2930, 1660, 1520, 1446, 1368, 1328, 1251, 1168, 1046, 756 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (s, 9 H), 3.06 (br s, 2 H), 4.39–4.41 (m, 1 H), 5.21 (br d, 1 H, *J* = 8.0 Hz), 5.72–5.84 (m, 1 H), 5.96–6.10 (m, 1 H), 7.17–7.33 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.3, 38.5, 55.3, 80.1, 126.8, 128.5, 129.2, 136.6, 155.3, 173.9.

MS: *m*/*z* (%) = 264 (M^+, 3), 230 (29), 191 (4), 164 (18), 147 (13), 120 (43), 91 (23), 73 (12), 57 (100).

HRMS: *m*/*z* calcd for $C_9H_{12}N_2O$: 264.1474; found: 264.1479.

To a solution of this product in EtOAc–MeOH (50:50, 6 mL) at 0 °C was added AcCl (2 mL). The resulting mixture was stirred for 30 min at 0 °C and the solvent was removed in vacuo (2 Torr, 45 °C) to give $PheNH_2$. Purification by flash column chromatography (40% EtOAc–hexane) gave product **22** (0.594 g, 71% overall yield).

(2*S*)-*N*-[(1*S*)-2-Amino-1-benzyl-2-oxoethyl]-2-[(*tert*-butoxycarbonyl)amino]-4-methylpentanamide (Boc-Leu-Phe-NH_2)

A solution of *N*-Boc-Leu **21** (0.948 g, 4.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.92 mmol), 1-hydroxybenzotriazole (467 mg, 3.92 mmol) and $NaHCO_3$ (598 mg) in DMF (15 mL) was stirred at r.t. for 1 h. To the resulting suspension was added amide **22** (638 mg, 3.92 mmol) at 0 °C and the mixture was stirred for 2 h at 0 °C and 18 h at r.t. The reaction mixture was diluted with EtOAc (25 mL) and the organic phase was washed with aq citric acid (pH 4), aq $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash column chromatography (40% EtOAc–hexane) gave the product.

Yield: 1.33 mg (86%); R_f 0.39 (70% EtOAc–hexane).

IR (KBr): 3063, 2957, 2922, 1935, 1502, 1453, 1367, 1253, 1168, 1099, 1042, 921, 870, 730 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.88 (d, 3 H, *J* = 6.4 Hz), 0.91 (d, 3 H, *J* = 6.4 Hz), 1.38 (s, 9 H), 1.45–1.62 (m, 3 H), 3.09 (d, 1 H, *J* = 6.6 Hz), 3.10–3.20 (m, 1 H), 4.06 (br s, 1 H), 4.74 (dd, 1 H, *J* = 15.0, 6.6 Hz), 5.13 (br s, 1 H), 6.02 (br s, 1 H), 6.65 (br s, 1 H), 7.05 (br s, 1 H), 7.19–7.31 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.9, 24.7, 28.3, 37.6, 41.0, 53.6, 53.8, 80.4, 126.8, 128.4, 129.1, 136.4, 155.7, 172.4, 173.4.

(1*S*,2*S*,4*R*)-{1-Benzyl-4-[1-(1*S*)-carbamoyl-2-phenylethylcarbamoyl)-(1*S*)-3-methylbutylcarbamoyl]-2-hydroxy-5-phenylpentyl}carbamic Acid *tert*-Butyl Ester (2)

To a solution of Boc-Leu-Phe-NH_2 (90 mg, 0.24 mmol) in EtOAc–MeOH (50:50, 3 mL) was added AcCl (1 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and the solvent was removed in vacuo (2 Torr, 45 °C) to give NH_2-Leu-Phe-NH_2 (**35**) in quantitative yield. A solution of **19** (62 mg, 0.117 mmol), NH_2-Leu-Phe-NH_2 (**35**; 63 mg, 0.23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (34 mg, 0.176 mmol), 1-hydroxybenzotriazole (21 mg, 0.176 mmol) and Et_3N (50 μL) in DMF (3 mL) was stirred at r.t. for 15 h. The reaction mixture was diluted with EtOAc (10 mL), and the organic phase was washed with aq citric acid (pH 4), aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash column chromatography (5% MeOH–CH_2Cl_2) gave the corresponding silylated product.

Yield: 83 mg (91%); $[\alpha]_D^{25}$ –32.6 (*c* = 0.57, MeOH); R_f 0.28 (60% EtOAc–hexane); mp 189.3–192.2 °C.

Silylated Product

IR (KBr): 3453, 3297, 3077, 3033, 2964, 2935, 2867, 1689, 1650, 1548, 1494, 1455, 1382, 1259, 1176, 1074, 844, 781, 703.

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.09 (s, 6 H), 0.70 (d, 3 H, *J* = 6.4 Hz), 0.78 (d, 3 H, *J* = 6.4 Hz), 0.94 (s, 9 H), 1.18–1.31 (m, 3 H), 1.33 (s, 9 H), 1.63 (m, 1 H), 1.75 (br t, 1 H, *J* = 11.0 Hz), 2.50 (dd, 1 H, *J* = 13.6, 4.0 Hz), 2.61–2.69 (m, 3 H), 2.72–2.81 (m, 2 H), 3.20 (dd, 1 H, *J* = 14.3, 5.5 Hz), 3.68 (dd, 1 H, *J* = 10.2, 3.82 Hz), 3.97 (dd, 1 H, *J* = 17.0, 7.63 Hz), 4.05 (dd, 1 H, *J* = 12.7, 7.63 Hz), 4.56 (m, 1 H), 4.75 (d, 1 H, *J* = 10.0 Hz), 5.65 (br s, 1 H), 5.92 (d, 1 H, *J* = 8.2 Hz), 6.31 (d, 1 H, *J* = 5.2 Hz), 6.45 (br s, 1 H), 7.04–7.10 (m, 4 H), 7.11–7.33 (m, 11 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = –4.5, –3.8, 18.0, 22.2, 22.3, 24.4, 25.9, 28.4, 36.8, 36.9, 37.2, 39.2, 40.5, 44.6, 53.1, 53.3, 53.6, 70.4, 79.6, 126.5, 126.6, 126.7, 128.5, 128.5, 128.7, 128.8, 128.9, 130.0, 137.0, 138.2, 139.4, 156.5, 171.2, 173.1, 175.7.

L-682,458 (2)

This material was dissolved in a solution of Bu_4NF in THF (1 M, 2 mL) and stirred at r.t. for 48 h. The reaction mixture was diluted with citric acid in Et_2O (pH 4) and the resulting precipitate was collected by filtration, washed, and dried in vacuo to give L-682,679 (**2**). Further purification by flash column chromatography (6% MeOH–CH_2Cl_2) gave L-682,679 (**2**) as a white solid.

Yield: 67 mg (94%); $[\alpha]_D^{25}$ –32.6 (*c* = 0.57, MeOH); mp 189.3–192.2 °C; R_f 0.43 (80% EtOAc–hexane).

IR (KBr): 3377, 3341, 3190, 2955, 2924, 2872, 2853, 1667, 1649, 1621, 1531, 1451, 1365, 1273, 1250, 1172, 1080, 743, 698 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ = 0.77 (d, 3 H, *J* = 6.4 Hz), 0.84 (d, 3 H, *J* = 6.4 Hz), 1.28 (s, 9 H), 1.20–1.35 (m, 2 H), 1.49 (m, 1 H), 1.60 (m, 1 H), 2.45 (dd, 1 H, *J* = 13.4, 8.2 Hz), 2.53 (dd, 1 H, *J* = 13.7, 9.5 Hz), 2.70 (dd, 1 H, *J* = 13.6, 5.0 Hz), 2.78–2.87 (m, 3 H), 3.00 (dd, 1 H, *J* = 5.2, 3.7 Hz), 3.51–3.57 (m, 1 H), 4.21 (q, 1 H, *J* = 6.7 Hz), 4.42 (q, 1 H, *J* = 5.5 Hz), 4.48 (d, 1 H, *J* = 6.1 Hz), 6.36 (d, 1 H, *J* = 9.0 Hz), 7.09 (br s, 1 H), 7.12–7.25 (m, 15 H), 7.34 (br s, 1 H), 7.70 (d, 1 H, *J* = 8.0 Hz), 7.93 (d, 1 H, *J* = 8.0 Hz).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 23.1, 24.2, 28.0, 28.4, 35.1, 36.3, 37.7, 38.9, 40.9, 43.7, 51.5, 53.5, 56.5, 69.4, 77.6, 125.9, 126.0, 126.4, 128.1, 128.2, 128.3, 129.1, 129.2, 129.4, 137.9, 139.8, 140.0, 155.5, 171.8, 172.8, 174.7.

(1*S*,4*R*){(1)-Benzyl-4-[1-(1*S*)-carbamoyl-2-phenylethylcarbamoyl)-(1*S*)-3-methylbutylcarbamoyl]-2-oxo-5-phenylpentyl}-carbamic Acid *tert*-Butyl Ester (4)

To a stirred solution of alcohol **2** (40 mg, 0.06 mmol) in DMF (1.5 mL) was added PDC (112 mg, 0.3 mmol) in one portion. The resulting reaction mixture was allowed to stirr at r.t. for 24 h. It was quenched with H_2O (10 mL), and extracted with EtOAc (2 × 15 mL). The organic layers were combined and dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash cromatography on silica gel (50% EtOAc–hexane) to provide the desired inhibitor L-684,414 (**4**) as a white solid.

Yield: 34 mg (85%); mp 173–176.8 °C; $[\alpha]_D^{25}$ –30.8 (*c* = 0.54, MeOH); R_f 0.41 (70% EtOAc–hexane).

IR (KBr): 3315, 3192, 3029, 2954, 1725, 1684, 1643, 1528, 1452, 1359, 1290, 1173, 1128, 826, 744, 697 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 0.80 (d, 3 H, *J* = 6.4 Hz), 0.88 (d, 3 H, *J* = 6.4 Hz), 1.27 (s, 9 H), 1.39 (m, 2 H), 1.57 (m, 1 H), 2.29 (dd, 1 H, *J* = 17.8, 4.1 Hz), 2.41 (dd, 1 H, *J* = 13.4, 9.4 Hz), 2.50 (br s, 1 H), 2.54 (dd, 1 H, *J* = 14.0, 11.0 Hz), 2.80–2.88 (m, 2 H), 2.91 (dd, 1 H, *J* = 13.6, 4.7 Hz), 2.96–3.07 (m, 2 H), 4.00 (m, 1 H), 4.20 (m, 1 H), 4.43 (m, 1 H), 7.08 (br s, 1 H), 7.12–7.28 (m, 16 H), 7.34 (br s, 1 H), 7.66 (d, 1 H, *J* = 7.6 Hz), 8.15 (d, 1 H, *J* = 7.9 Hz).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 21.6, 23.1, 24.1, 27.7, 28.2, 34.6, 37.6, 37.9, 40.7, 41.8, 51.4, 53.4, 61.0, 78.3, 126.2, 126.3, 128.1, 128.2, 128.3, 129.0, 129.1, 129.2, 129.3, 137.7, 138.4, 139.4, 155.5, 171.8, 172.7, 173.9, 208.5.

HRMS: *m*/*z* calcd for $C_{39}H_{50}N_4O_6$: 670.3730, found: 670.3718.

(3*R*,5*R*)-3-Benzyl-5-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}dihydrofuran-2-(3*H*)-one (44)

To a solution of amino alcohol **39** (0.560 g, 1.47 mmol) in THF (20 mL) cooled to 0 °C was added $BH_3{\cdot}SMe_2$ complex (4 mL of a 2 M solution in THF, 8 mmol). This mixture was stirred at 0 °C until complete consumption of starting material, as determined by TLC (ca. 24 h). EtOH (19 mL) was added followed by a 3 M solution of NaOH (20 mL) and 30% H_2O_2 (15 mL). The mixture was stirred at r.t. for 10 h. EtOAc (50 mL) was added and the organic layer was separated and washed with aq 10% Na_2SO_3 (50 mL) and brine (5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (50% EtOAc–hexane) gave a mixture of diols **42** and **43** (545 mg, 93%) as a colorless oil. Solid TPAP (46.5 mg, 0.14 mmol) was added in one portion to a stirred mixture of the diols **42** and **43** (545 mg, 1.36 mmol), followed by a suspension of NMO (465 mg, 4.3 mmol) and activated powdered molecular sieves (665 mg) in CH_2Cl_2 (15 mL) at r.t. under argon. On completion, the mixture was filtered through a pad of silica gel, eluting with hexane–EtOAc (93:07). The filtrate was evaporated and the residue was purified by column chromatography on silica gel using 7% EtOAc–hexane to give 308 mg and 227 mg of lactones **44** and **45**, respectively, in 97% overall yield.

Yield: 0.308 g (53%); mp 123–124.5 °C; $[\alpha]_D^{25}$ –70.0 (*c* = 1.0, $CHCl_3$); R_f 0.60 (30% EtOAc–hexane).

IR (KBr): 3397, 3025, 2996, 2930, 1785, 1696, 1608, 1513, 1336, 1259, 1172, 1101 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (s, 9 H), 1.72–1.84 (m, 1 H), 2.17–2.27 (m, 1 H), 2.66–2.95 (m, 4 H), 3.26 (dd, 1 H, *J* = 13.6, 4.0 Hz,), 3.88 (br s, 1 H), 4.26 (br s, 1 H), 4.42 (br d, 1 H, *J* = 7.3 Hz), 7.15–7.32 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.2, 29.7, 31.4, 36.1, 45.5, 54.3, 78.9, 79.8, 126.6, 128.4, 128.5, 128.6, 129.3, 136.4, 138.2, 155.0, 177.4.

(2*R*,4*R*,5*S*)-2-Benzyl-5-*tert*-butoxycarbonylamino-4-(*tert*-butyldimethylsilyloxy)-6-phenylhexanoic Acid (46)

A solution of **44** (0.21 g, 5.3 mmol) in 1,2-dimethoxyethane (36 mL) was treated with a solution of LiOH in H_2O (1 M, 36 mL, 36 mmol) and stirred at r.t. for 6 h. The reaction mixture was carefully acidified to pH 4 with aq citric acid, and then extracted with EtOAc. The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude hydroxy acid (0.216 g) was dissolved in DMF (30 mL), treated with *tert*-butyldimethylsilyl chloride (7.98 g, 52.8 mmol) and imidazole (4.26 g, 0.06 mol). The solution was stirred for 15 h. The mixture was diluted with MeOH (6 mL), stirred for 3 h, and then evaporated in vacuo. The mixture was partitioned between aq citric acid and EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash column chromatography (3% MeOH–CH_2Cl_2) gave **46** (204 mg, 73%) as a white foam.

Yield: 204 mg (73%); $[\alpha]_D^{25}$ –12.8 (c 1.03, $CHCl_3$); R_f 0.54 (30% EtOAc–hexane).

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.81 (s, 9 H), 1.23 (s, 9 H), 1.51–1.80 (m, 2 H), 2.51–2.75 (m, 5 H), 3.54–3.75 (m, 2 H), 6.44 (d, 1 H, *J* = 8.8 Hz), 7.05–7.25 (m, 10 H), 12.06 (m, 1 H).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = –2.4, 20.1, 28.2, 30.4, 39.9, 41.1, 45.5, 58.6, 74.0, 79.8, 128.0, 128.5, 130.4, 130.6, 131.0, 131.2, 141.8, 147.8, 157.4, 178.4;

(1*S*,2*R*,4*R*)-{1-Benzyl-4-[1-(1*S*)-carbamoyl-2-phenylethylcarbamoyl)-(1*S*)-3-methylbutylcarbamoyl]-2-hydroxy-5-phenylpentyl}carbamic Acid *tert*-Butyl Ester (3)

To a solution of Boc-Leu-Phe-NH_2 (91.3 mg, 0.24 mmol) in EtOAc–MeOH (50:50, 3 mL) at 0 °C was added AcCl (1 mL). The resulting mixture was stirred for 30 min at 0 °C and the solvent was removed in vacuo (2 Torr, 45 °C) to give NH_2-Leu-Phe-NH_2 (**35**) in quantitative yield. A solution of **46** (100 mg, 0.19 mmol), H_2NLeu-Phe-NH_2 (**35**) (63 mg, 0.23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (51 mg, 0.27 mmol) and 1-hydroxybenzotriazole (36 mg, 0.26 mmol) in DMF (5 mL) was stirred at r.t. for 15 h. The reaction mixture was diluted with EtOAc (10 mL), and the organic phase was washed with aq citric acid (pH 4), aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash column chromatography (5% MeOH–CH_2Cl_2) gave the the corresponding silylated product.

Yield: 135 mg (91%); R_f 0.5 (70% EtOAc–hexane).

Silylated Product

IR (KBr): 3453, 3386, 3303, 3065, 2960, 2926, 2861, 1647, 1496, 1458, 1370, 1252, 1164, 1097, 743 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = –0.05 (s, 3 H), –0.03 (s, 3 H), 0.69 (d, 3 H, *J* = 6.4 Hz), 0.74 (d, 3 H, *J* = 6.4 Hz), 0.83 (s, 9 H), 1.18–1.36 (m, 3 H), 1.26 (s, 9 H), 1.57 (m, 1 H), 1.76 (m, 1 H), 2.39 (dd, 1 H, *J* = 14.8, 9.92 Hz), 2.45 (m, 1 H), 2.57–2.65 (m, 1 H), 2.67 (dd, 1 H *J* = 8.85, 6.7 Hz), 2.77 (dd, 1 H, *J* = 14.3, 8.2 Hz), 3.04 (m, 1 H), 3.10 (dd, 1 H, *J* = 14.2, 5.6 Hz), 3.63 (m, 1 H), 3.72 (m, 1 H), 4.07 (m, 1 H), 4.56 (m, 2 H), 5.41 (br s, 1 H), 5.95 (d, 1 H, *J* = 8.2 Hz), 6.37 (br s, 1 H), 6.68 (br d, 1 H, *J* = 4.6 Hz), 6.92 (d, 1 H, *J* = 7.3 Hz), 7.05–7.26 (m, 15 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = –5.0, –4.5, 18.0, 22.3, 22.4, 24.5, 25.8, 28.4, 36.7, 36.8, 38.1, 38.7, 40.3, 44.8, 53.3, 53.5, 54.2, 71.8, 79.6, 126.3, 126.7, 126.9, 127.3, 128.4, 128.6, 128.7, 128.9, 129.0, 136.9, 138.6, 139.0, 155.8, 171.4, 173.1, 176.0.

This material was dissolved in a solution of Bu_4NF in THF (1 M, 1.25 mL) and the solution was stirred at r.t. for 12 h. The reaction mixture was diluted with citric acid in Et_2O (pH 4) and the resulting precipitate was collected by filtration, and dried in vacuo to give L-685,458 (**3**). Further purification by flash column chromatography (6% MeOH–CH_2Cl_2) gave L-685,458 (**3**) as a white solid.[47]

Yield: 96 mg (75%); mp 212–213 °C; $[\alpha]_D^{25}$ –27.5 (*c* = 0.5, $CHCl_3$); R_f 0.43 (80% EtOAc–hexane).

L-685,458 (3)

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 0.76 (d, 3 H, *J* = 6.9 Hz), 0.82 (d, 3 H, *J* = 6.6 Hz), 1.24 (s, 9 H), 1.26–1.41 (m, 2 H), 1.47–1.67 (m, 3 H), 2.43 (dd, 1 H, *J* = 13.4, 10.7 Hz), 2.54 (dd, 1 H, *J* = 13.6, 6.5 Hz), 2.64–2.85 (m, 4 H), 3.00 (dd, 1 H, *J* = 13.7, 5.2 Hz), 3.39–3.42 (m, 2 H), 4.14–4.19 (m, 1 H), 4.38–4.40 (m, 1 H), 4.74 (d, 1 H, *J* = 5.8 Hz), 6.49 (d, 1 H, *J* = 9.2 Hz), 7.07–7.24 (m, 16 H), 7.31 (br s, 1 H), 7.65 (d, 1 H, *J* = 8.5 Hz), 7.91 (d, 1 H, *J* = 8.0 Hz).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 19.1, 21.8, 23.2, 24.1, 28.4, 35.5, 35.9, 37.7, 40.8, 44.6, 51.6, 53.6, 56.7, 71.4, 77.5, 125.7, 126.0, 126.3, 128.0, 128.15, 128.2, 129.0, 129.2, 129.3, 137.9, 139.9, 140.2, 155.3, 171.9, 172.8, 175.06.[47]

Compound 3 From Ketone 4

$LiBH_4$ (127 mg, 0.50 mmol) was dissolved in EtOH (4 mL) at –5 °C under N_2, and then a solution of ketone **4** (0.25 mmol) in EtOH (3 mL) was added dropwise. After 24 h, the solution was quenched with H_2O (2 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by flash column chromatography (6% MeOH–CH_2Cl_2) to give L-685,458 (**3**) as a white solid.

Yield: 93%.[18,46,47]

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