

Asymmetric Total Synthesis of the Gastroprotective Microbial Agent AI-77-B

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An enantioselective total synthesis of the pseudopeptide microbial agent AI-77-B, which has shown potent antiulcerogenic properties, is described. The synthesis is convergent and involves the assembly of a dihydroisocoumarin fragment and a hydroxy amino acid. The dihydroisocoumarin derivative was synthesised by means of a Diels–Alder reaction between 1-methoxy-1,3-cyclohexadiene and an alkynyl ester derivative as the dienophile. The alkynyl ester was obtained stereoselectively by two different synthetic routes: (1) A stereoselective allylation of leucinal, and (2) a titanium enolate-mediated

anti-aldol reaction with trichlorobutylaldehyde, a novel homopropargylaldehyde equivalent. The stereocentres of the hydroxy amino acid moiety were generated through a titanium enolate-mediated *syn*-aldol reaction, Curtius rearrangement, and application of Dondoni's aldehyde homologation. Condensation of the dihydroisocoumarin and hydroxy amino acid moieties and subsequent removal of the protecting groups furnished optically active AI-77-B. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2003)

Introduction

The 3,4-dihydroisocoumarin derivatives are common structural features of numerous natural products and exhibit a wide range of important biological properties.^[1,2] One such natural product, AI-77-B (**1**, Figure 1), which contains a 3,4-dihydroisocoumarin linked to a dihydroxy β -amino acid side chain, has shown significant antiulcerogenic properties. AI-77-B (**1**) has been isolated from the culture broth of *Bacillus pumilus* AI-77.^[3]

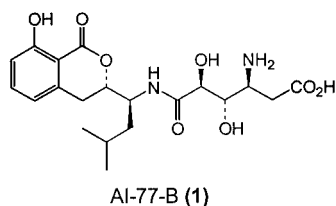


Figure 1. Structure of AI-77-B

AI-77-B is a highly fluorescent pseudopeptide, the structure and absolute configuration of which were determined by Shimojima and co-workers by spectroscopic and X-ray crystallographic techniques.^[4–6] It exhibits potent antiulcerogenic and simultaneous antiinflammatory activity toward stress ulcers without anticholinergic and antihistaminergic side effects.^[4–6] The therapeutic potential of AI-77-B is, however, limited by its poor oral absorption properties. Because of its intriguing biological properties, there has been significant interest in the synthesis and structural mo-

dification of AI-77-B. These efforts culminated in the development of a number of orally active prodrug analogues possessing both antiinflammatory and antiulcer activities.^[7,8] To date, several total syntheses of AI-77-B have been reported, as well as synthetic approaches to either the dihydroisocoumarin or the hydroxy amino acid fragment.^[9–24] The majority of these previously described syntheses utilised chirality derived from D-ribose,^[9] L-leucine,^[10–16] L-aspartic acid^[10,11,13,14] and D-glutamic acid.^[15,16] We have recently reported a stereoselective route to AI-77-B in which four of the five stereogenic centres were set by asymmetric synthesis.^[25,26] Here we now describe a convergent and stereocontrolled total synthesis of AI-77-B in which all five stereogenic centres have been constructed by asymmetric synthesis.

Results and Discussion

Our synthetic plan for AI-77-B (**1**) is based upon coupling the dihydroisocoumarin fragment **2** and the protected hydroxy amino acid **3** and subsequent conversion of the terminal olefin into a carboxylic acid at the final stage of the synthesis. As outlined in Figure 2, the dihydroisocoumarin skeleton would be constructed by means of a thermal Diels–Alder reaction between dienophile **4** and 1-methoxy-1,3-cyclohexadiene. This reaction generally proceeds with extrusion of ethylene, providing convenient access to aromatic compounds.^[27–29] Alkyne derivative **4** should be accessible from *anti*-aldol product **5** through Curtius rearrangement and base-catalysed elimination of the trihaloalkane functionality. Both stereogenic centres in **4** would be derived by the diastereoselective *anti*-aldol methodology recently developed by our group.^[30,31] Alternatively, con-

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struction of alkyne derivative **4** could be carried out by starting with leucinal, through stereoselective allylation followed by conversion of the allyl group into a terminal alkyne derivative. The synthesis of hydroxy amino acid fragment **3** should be achievable from isopropylidene derivative **6** through Dondoni's homologation procedure,^[32–34] and the 1,2-amino alcohol functionality in **6** should be derivable from *syn*-aldol product **7** by use of a Curtius rearrangement as the key step. Our recently developed highly diastereoselective *syn*-aldol reaction can be employed to provide **7**,^[26] therefore four of the five stereogenic centres in AI-77-B can be efficiently constructed by means of our ester-derived titanium enolate-based aldol reactions.

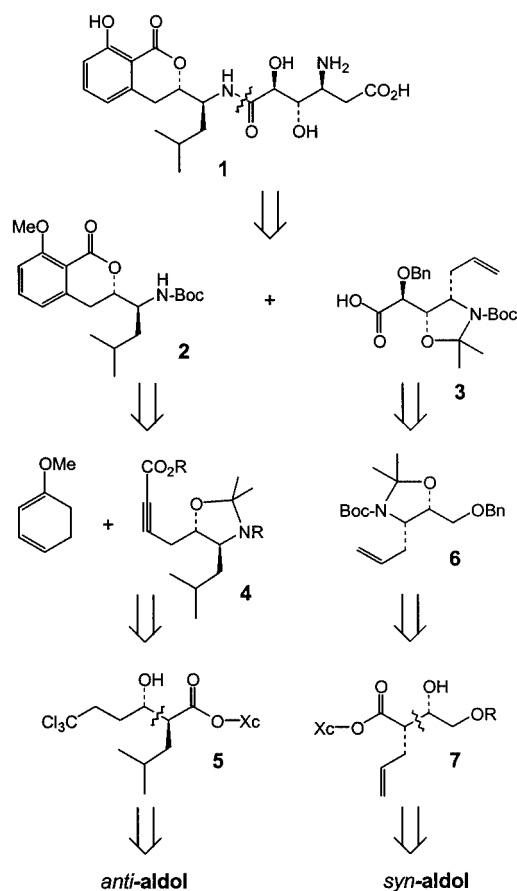
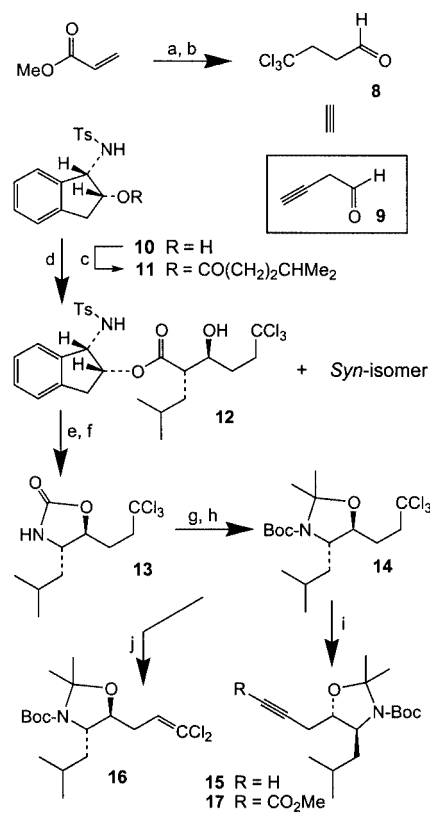


Figure 2. Retrosynthesis of AI-77-B

It was intended that initial assembly of dihydroisocoumarin fragment **2** should be carried out prior to the construction of hydroxy amino acid moiety **3**. We planned to use an ester-derived titanium enolate-mediated *anti*-aldol reaction to construct both stereocentres of aldolate **5**.^[30] The terminal trichloroalkyl group in **5** was designed to provide alkyne functionality through a base-catalysed elimination reaction. As shown in Scheme 1, the requisite trichlorobutyr-aldehyde (**8**) is a homopropargyl aldehyde (**9**) equivalent. Multigram quantities of aldehyde **8** were prepared by Michael addition of chloroform to methyl acrylate under catalytic phase-transfer conditions with NaOH and BnEt₃NCl in CHCl₃/water (1:1) at 0 °C for 2 h to provide

the corresponding methyl trichlorobutyrate in 32% yield after distillation.^[35]



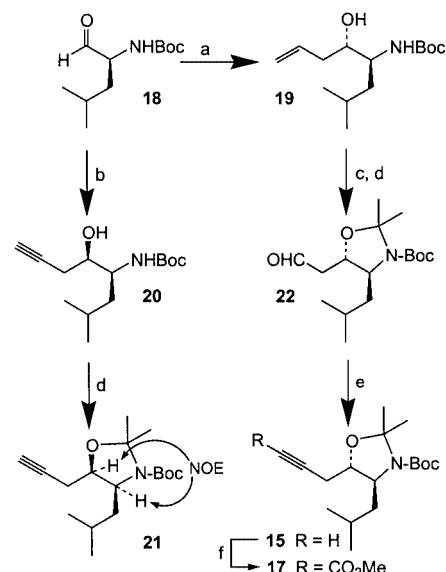
Scheme 1. (a) NaOH, BnEt₃NCl, CHCl₃, H₂O, 0 °C, 2 h (32%); (b) DIBAL, CH₂Cl₂, –78 °C, 1.5 h (95%); (c) 4-methylvaleric acid, EDCI, DMAP, 23 °C, 2 h (99%); (d) TiCl₄, *i*Pr₂NEt, 0 to 23 °C, 1 h, then **8**, –78 °C, 10 min (90%, 90% *de*); (e) LiOH, H₂O₂, THF, H₂O, room temp., 12 h (97%); (f) DPPA, Et₃N, CH₂Cl₂, reflux, 12 h, (94%); (g) Boc₂O, DMAP, Et₃N, THF, room temp., 3 h, then NaOH, EtOH, H₂O, room temp., 5 min (91%); (h) DMP, TsOH, CH₂Cl₂, 23 °C, 15 min (97%); (i) *n*BuLi, TMEDA, THF, –78 °C, 20 min, then ClCO₂Me (85%); (j) *n*BuLi, THF, –78 °C, 10 min (88%)

Subsequent reduction of the ester with DIBAL in CH₂Cl₂ at –78 °C afforded aldehyde **8** in 95% yield. For the ester enolate aldol reaction, the requisite optically active indanyl ester **11** was prepared by esterification of the known *N*-tosyl-1-amino-2-indanol^[36] **10** with 4-methylvaleric acid in the presence of EDCI for 2 h at 23 °C, which furnished **11** in near quantitative yield. The preparation of ester **11** was also accomplished in a one-pot procedure, by consecutive tosylation and acylation of the commercially available (1*S*,2*R*)-1-aminoindan-2-ol with TsCl and 2 equiv. of DMAP in CH₂Cl₂ at 0 °C for 1 h, followed by esterification with 4-methylvaleric acid in the presence of EDCI for 2 h at 23 °C, to afford **11** in 99% yield. The aldol condensation of **11** was carried out by initial treatment of **11** with TiCl₄ and *i*Pr₂NEt in CH₂Cl₂ at 0 to 23 °C for 1 h. The resulting titanium enolate was then cooled to –78 °C and treated with aldehyde **8** at –78 °C for 10 min to give aldolate **12** as the major product (*anti*/*syn* = 19:1 by ¹H and ¹³C NMR analysis) in 90% yield after silica gel chromatography. Saponification of **12** with aqueous LiOH and H₂O₂ in THF/water (3:1) for 12 h at 23 °C provided the corresponding

acid. The chiral auxiliary was recovered in 95% yield after column chromatography. Curtius rearrangement^[37–39] of the resulting acid was carried out with diphenylphosphoryl azide and triethylamine in CH_2Cl_2 at reflux for 12 h, to furnish oxazolidinone derivative **13** as a single diastereomer in 94% yield.^[40] Treatment of oxazolidinone **13** with Boc_2O and Et_3N in the presence of a catalytic amount of DMAP in THF at 23 °C for 3 h, followed by treatment with aqueous NaOH in EtOH/water (1:1) for 5 min, afforded the corresponding *N*-Boc-protected amino alcohol. Subsequent protection of the resulting amino alcohol with 2,2-dimethoxypropane and *p*-TsOH in CH_2Cl_2 for 15 min at 23 °C provided isopropylidene derivative **14** in 88% yield. Our synthetic strategy now called for the conversion of the trichloro moiety of **14** into an alkyne, resulting in **17**, the dienophile for the key Diels–Alder reaction. Our initial attempt to generate the terminal alkyne functionality by treatment of **14** with *n*BuLi (3–6 equiv.) in THF at –78 °C furnished only a trace amount of terminal alkyne **15**, together with mostly undesired by-products. However, treatment of **14** with 1.5 equiv. of *n*BuLi in THF at –78 °C for 10 min gave dichloroolefin **16** in excellent yield. Treatment of **14** with *n*BuLi (4 equiv.) and TMEDA (3 equiv.) afforded the alkyne derivative **15** in 88% yield. Subsequently, trichloro derivative **14** was converted into dienophile **17** in a one-pot procedure, **14** being treated at –78 °C first with *n*BuLi (1.5 equiv.), and then with TMEDA (3 equiv.) and *n*BuLi (3 equiv.). The resulting reaction mixture was quenched with methyl chloroformate to provide the required dienophile **17** in 85% yield.

An alternative synthesis of dienophile **17** was also accomplished by means of a diastereoselective allylmethyl addition to *N*-Boc-leucinal **18**.^[26] This was prepared in multigram quantities from the commercial *N*-Boc-L-leucine by formation and reduction of the corresponding Weinreb amide.^[41,42] Rich and Prasad have shown that the SnCl_4 -mediated, highly diastereoselective allylsilane addition to **18** provides the *threo* isomer **19**.^[43] In a modified procedure, the use of allyltributyltin in place of allylsilane provided further improvements in the yield of and selectivity for *threo* isomer **19**. As shown in Scheme 2, treatment of **18** with SnCl_4 at –78 °C, followed by dropwise addition of allyltributyltin in CH_2Cl_2 , provided homoallylic alcohol **19** as a major product (96:4 mixture by ^1H NMR analysis).

The presence of tin impurities, however, greatly complicated the purification of pure diastereomer **19**. This problem was circumvented by reduction of the crude product with NaBH_4 in MeOH for 2 min at 23 °C, which presumably reduced the chloroalkylstannane impurities in the crude product to alkylstannane derivatives.^[45] This procedure significantly simplified the chromatographic separation, and diastereomer **19** was isolated in 90% yield. For the stereoselective synthesis of the corresponding terminal alkyne derivative of **19**, we have also investigated the addition to **18** of organozinc reagents derived from propargyl bromide.^[26] Treatment of *N*-Boc-leucinal with 4 equiv. of propargyl bromide in DMF/diethyl ether (1:1), followed by slow addition of zinc dust at 0 °C, afforded homopropargyl alcohol



Scheme 2. (a) SnCl_4 , allyltributyltin, –78 °C, 1 h (94%, 92% *de*); (b) $\text{HC}\equiv\text{CCH}_2\text{Br}$, Zn, DMF/ Et_2O (1:1), 0 to 23 °C, 12 h (67%, 84% *de*); (c) DMP, TsOH, DCM, 23 °C, 1 h (99%); (d) O_3 , PPh_3 , DCM, –78 °C (97%); (e) $\text{CH}_3\text{COC}(\text{N}_2)\text{PO}(\text{OMe})_2$, Cs_2CO_3 , *i*PrOH, 0 °C, 1 h, 23 °C, 11 h (97%); (f) *n*BuLi, ClCO_2Me , THF, –78 °C, 10 min (99%)

20 as the major product, in 67% yield. ^1H and ^{13}C NMR analysis revealed a diastereomeric ratio of 92:8. The depicted stereochemical identity of the major isomer **20** was established after its conversion into the isopropylidene derivative **21** and subsequent NOE experiments.

The stereochemical outcome of the allyltributyltin addition to **18** can be explained on the basis of the chelated transition state model shown in Figure 3. In this model, SnCl_4 forms a conformationally constrained chelated complex in which the presence of the bulky isobutyl group controls the direction of the incoming nucleophile. Preferential *Si*-face attack thus results in the observed *syn* stereoselectivity. Similar allylmethyl addition to α -aminoaldehydes has previously been studied by Kiyooka et al. and Rich et al.^[43,44]

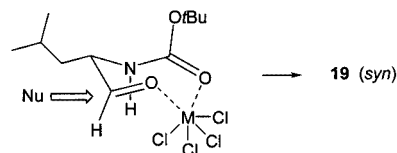
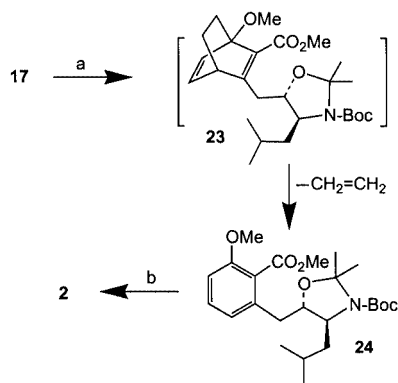


Figure 3. Stereochemical model for allylmethyl addition

For the synthesis of dienophile **17**, homoallylic alcohol **19** was treated with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TsOH at 23 °C for 1 h, followed by ozonolytic cleavage of the resulting olefin at –78 °C to provide **22** in 96% yield. Treatment of aldehyde **22** with dimethyl (1-diazo-2-oxopropyl)phosphonate^[46–49] in the presence of Cs_2CO_3 in 2-propanol at 0–23 °C for 11 h provided alkyne derivative **15** in 97% yield. The terminal alkyne was deprotonated with *n*BuLi in THF at –78 °C for 10 min and the resulting lithium acetylide was quenched

with methyl chloroformate at $-78\text{ }^{\circ}\text{C}$ to furnish the alkynyl ester **17** in near quantitative yield.

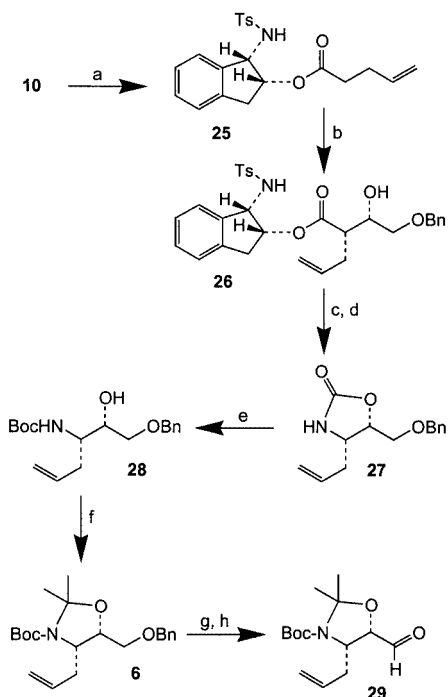
With an efficient synthesis of dienophile **17** now available, we next planned to carry out the key Diels–Alder step. As shown in Scheme 3, the Diels–Alder reaction between **17** and excess 1-methoxy-1,3-cyclohexadiene (10 equiv.) was carried out in toluene in a sealed tube at $175\text{ }^{\circ}\text{C}$ bath temperature for 72 h. The cycloaddition presumably proceeded to form cycloadduct **23**, which then underwent a retro-Diels–Alder reaction with the extrusion of ethylene. This provided benzoate derivative **24** in 76% yield after silica gel chromatography. Treatment of **24** with a catalytic amount of *p*-TsOH and water in CH_2Cl_2 for 20 min at $23\text{ }^{\circ}\text{C}$ furnished 3,4-dihydroisocoumarin fragment **2** in 97% yield.^[26]



Scheme 3. (a) 1-Methoxy-1,3-cyclobutadiene, toluene, $175\text{ }^{\circ}\text{C}$, 3 d (76%); (b) TsOH, CH_2Cl_2 , H_2O , $23\text{ }^{\circ}\text{C}$, 20 min (97%)

The synthesis of protected hydroxyamino acid fragment **3** is shown in Scheme 4. We have recently developed practical asymmetric methodologies for the preparation of optically active *syn*- and *anti*-aldols based upon ester-derived titanium enolate aldol reactions.^[30,31] We planned to utilise our ester-derived titanium enolate-mediated *syn*-aldol condensation with benzyloxyacetaldehyde to generate the stereocentres of aldolate **7**. Thus, acylation of *cis*-1-toluenesulfonamido-2-indanol **10** with 4-pentenoic acid in the presence of EDCI and DMAP afforded ester **25** in excellent yield.

The corresponding titanium enolate was generated by treatment of ester **25** with TiCl_4 and $i\text{Pr}_2\text{NEt}$ in CH_2Cl_2 at $0\text{--}23\text{ }^{\circ}\text{C}$ for 1 h. The resulting enolate was treated with benzyloxyacetaldehyde at $-78\text{ }^{\circ}\text{C}$ to provide *syn*-aldolate **26** as a single diastereomer in 97% yield after chromatography. Aldolate **26** was converted into oxazolidinone **27** in a two-step sequence. Saponification with lithium hydroxide in the presence of hydrogen peroxide in THF/water (3:1) provided the corresponding acid (97%), with recovery of the chiral auxiliary (92%). The Curtius rearrangement^[37–39] of the resulting acid was carried out with diphenylphosphoryl azide and triethylamine in CH_2Cl_2 at reflux for 12 h. This afforded oxazolidinone **27** in 92% yield as a single isomer by ^1H and ^{13}C NMR analysis.^[40] Treatment of **27** with Boc_2O and triethylamine in the presence of a catalytic

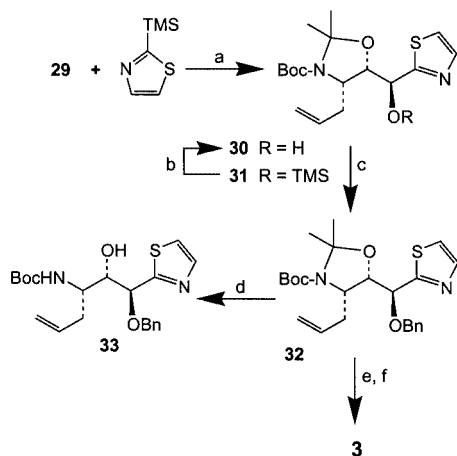


Scheme 4. (a) 4-Pentenoic acid, EDCI, DMAP, CH_2Cl_2 , $23\text{ }^{\circ}\text{C}$, 4 h (99%); (b) TiCl_4 , $i\text{Pr}_2\text{NEt}$, $0\text{ to }23\text{ }^{\circ}\text{C}$, 1 h, then BnOCH_2CHO , $-78\text{ }^{\circ}\text{C}$, 20 min (97%); (c) LiOH , H_2O_2 , $\text{THF}/\text{H}_2\text{O}$ (3:1), $23\text{ }^{\circ}\text{C}$, 12 h (96%); (d) DPPA, Et_3N , CH_2Cl_2 , reflux, 12 h (92%); (e) Boc_2O , Et_3N , DMAP, THF, $23\text{ }^{\circ}\text{C}$, 2 h, then aqueous NaOH/EtOH (1:1) (96%); (f) DMP, *p*-TsOH, CH_2Cl_2 , $23\text{ }^{\circ}\text{C}$, 6 h (92%); (g) Li/NH_3 , THF, $-78\text{ }^{\circ}\text{C}$, 5 min (95%); (h) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , $-78\text{ to }0\text{ }^{\circ}\text{C}$ (95%)

amount of DMAP in THF at $23\text{ }^{\circ}\text{C}$ for 2 h provided the corresponding *N*-Boc-oxazolidinone derivative, which was hydrolysed with aqueous sodium hydroxide in EtOH/water (1:1) to furnish *N*-Boc-protected amino alcohol **28** in 96% yield. Treatment of **28** with 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH in CH_2Cl_2 at $23\text{ }^{\circ}\text{C}$ afforded *N,O*-isopropylidene derivative **6** in 92% yield. Removal of the benzyl ether was effected by reduction of **6** with lithium in liquid ammonia at $-78\text{ }^{\circ}\text{C}$ for 5 min, and Swern oxidation of the resulting alcohol afforded aldehyde **29**, which was subjected to Dondoni's stereoselective homologation procedure.^[32–34]

As depicted in Scheme 5, treatment of aldehyde **29** with 2-(trimethylsilyl)thiazole in CH_2Cl_2 at $23\text{ }^{\circ}\text{C}$ for 6 h furnished a 1:1 mixture of alcohol **30** and its trimethylsilyl ether derivative **31**. Immediate exposure of the reaction mixture to $n\text{Bu}_4\text{N}^+\text{F}^-$ at $23\text{ }^{\circ}\text{C}$ for 20 min afforded **30** in 85% yield. The determination of the isomer ratio by ^1H NMR (CDCl_3 or $[\text{D}_6]\text{DMSO}$, including low-temperature experiments) was complicated by the presence of the *N*-Boc-*O*-isopropylidene group, which resulted in rotational isomers at $23\text{ }^{\circ}\text{C}$. However, the level of diastereoselectivity was determined unequivocally after protection of **30** as its benzyl ether **32** and subsequent removal of the isopropylidene group to provide *N*-Boc derivative **33**. The ^1H and ^{13}C NMR analysis of **33** revealed the presence of a single diastereomer. Our next synthetic plan required the conversion of the thiazole moiety of **32** into an aldehyde, followed

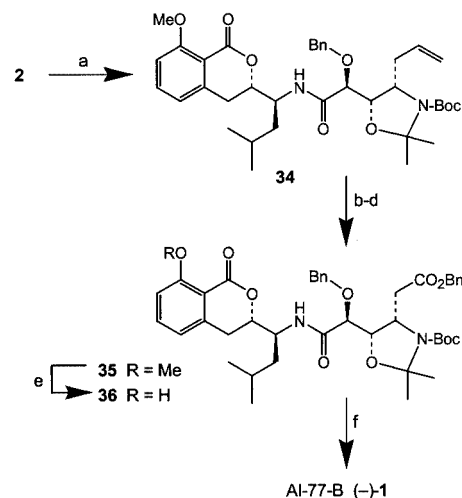
by its oxidation to hydroxy amino acid fragment **3**. The thiazole group was first converted into an aldehyde in a one-pot, three-step sequence developed by Dondoni et al.^[32–34] Accordingly, thiazole **32** was *N*-methylated by treatment with methyl trifluoromethanesulfonate in the presence of molecular sieves in acetonitrile at 23 °C for 30 min. The resulting thiazolinium C=N bond was reduced with sodium borohydride in MeOH at 0 °C for 30 min to provide the corresponding thiazolidine. Subsequent treatment of the thiazolidine with copper(II) oxide and copper(II) chloride in a mixture of acetonitrile and water (10:1) afforded the α -benzyloxyaldehyde in an overall yield of 82%. The more commonly used mercury(II) chloride procedure was less effective, as it converted the thiazolidine to α -benzyloxyaldehyde in only modest yields (25–35%). The α -benzyloxyaldehyde was oxidized with sodium chlorite in *tert*-butyl alcohol/water (5:1) in the presence of 2-methyl-2-butene to furnish **3** in 98% yield.



Scheme 5. (a) 2-TST, CH₂Cl₂, 23 °C, 6 h; (b) TBAF, THF, room temp., 20 min (85%, **29** to **30**); (c) NaH, BnBr, *n*Bu₄NI, THF, 12 h (95%); (d) *p*-TsOH·H₂O, MeOH, 23 °C, 24 h (95%); (e) *i.* MeOTf, 4 Å molecular sieves, MeCN, 23 °C, 30 min; *ii.* NaBH₄, MeOH, 0 °C, 30 min; *iii.* CuO, CuCl₂·H₂O, MeCN/H₂O (10:1), 23 °C, 10 min (82%); (f) NaClO₂, NaH₂PO₄·H₂O, 2-methyl-2-butene, *t*BuOH/H₂O (5:1) (98%)

With the efficient synthesis of isocoumarin fragment **2** and hydroxyamino acid fragment **3** now accomplished, our synthetic efforts were then focused on coupling these fragments. As shown in Scheme 6, the free amine of isocoumarin **2** was generated by treatment with trifluoroacetic acid in CH₂Cl₂ at 0 °C for 30 min, followed by concentration of the reaction mixture to dryness. Since the free amine readily transforms into the corresponding lactam upon standing, the coupling reaction was carried out immediately with its ammonium salt.^[4] This was treated with acid **3** in the presence of EDCI and DMAP in CH₂Cl₂ at 23 °C for 12 h to furnish the amide derivative **34** in 72% yield.

As shown, the terminal alkene in **34** was converted into the benzyl ester derivative by the following three-step sequence: (1) ozonolysis at –78 °C to furnish the corresponding aldehyde, (2) oxidation of the resulting aldehyde to an acid by exposure to sodium chlorite in a mixture of *tert*-



Scheme 6. (a) TFA, CH₂Cl₂, 0 °C, 30 min, then **3**, EDCI, DMAP, CH₂Cl₂, room temp., 12 h (72%); (b) O₃, CH₂Cl₂, –78 to 23 °C, PPh₃ (98%); (c) NaClO₂, 2-methyl-2-butene, NaH₂PO₄·H₂O, *t*BuOH/H₂O (5:1) (99%); (d) Cs₂CO₃, MeOH/H₂O (5:1), 30 min, then BnBr, DMF, 0 °C, 6 h (90%); (e) MgI₂, THF, reflux, 5 min (93%); (f) H₂, 10% Pd/C, Dowex® 50-X8, THF/MeOH (1:1), 23 °C, 12 h (75%)

butyl alcohol and water (5:1) in the presence of 2-methyl-2-butene, and (3) treatment of the resulting acid with cesium carbonate and benzyl bromide to provide benzyl ester **35** in 87% yield over three steps. For clean *O*-demethylation, the formation of benzyl ester **35** was critical, as attempted *O*-demethylation of the corresponding acid with MgI₂ in THF resulted in numerous side products and a low yield (15–25%) of the desired phenol derivative. Smooth *O*-demethylation was effected by treatment of **35** with MgI₂ in THF, followed by heating the resulting mixture at reflux for 5 min to afford phenol derivative **36** in 93% yield.^[11]

The completion of the synthesis of AI-77-B now required the removal of the remaining protecting groups. We initially attempted sequential removal of the protecting groups, but this proved to be more difficult than we had expected. After much experimentation, we developed conditions that effectively removed all three protecting groups in a one-pot procedure. Thus, phenol derivative **36** in THF/MeOH (1:1) was treated with 10% Pd/C and Dowex® 50-X8 resin at 23 °C under hydrogen for 12 h. This resulted in clean removal of the isopropylidene, *tert*-butoxycarbonyl and benzyl groups, providing optically active AI-77-B in 75% yield {[α]_D²³ = –75.2 (*c* = 0.11, MeOH); ref.^[15,16] [α]_D²² = –78.2 (*c* = 0.08, MeOH); m.p. 134–135 °C; ref.^[4] m.p. 139.5 °C}. The spectral data for synthetic AI-77-B are in full accordance with the reported data for authentic samples.^[4,10,11]

Conclusion

In summary, a stereocontrolled and convergent synthesis of the gastroprotective substance AI-77-B has been achieved. A number of key features of this synthesis are noteworthy. All five stereogenic centres of AI-77-B were set up by asymmetric syntheses. The synthesis features highly diastereoselec-

tive ester-derived asymmetric *syn*- and *anti*-aldol reactions, a regioselective Diels–Alder reaction, and Dondini homologation. This synthesis should provide convenient access to a variety of structural analogues of AI-77-B.

Experimental Section

General: Melting points were recorded with a Thomas Hoover capillary melting point apparatus and are uncorrected. Anhydrous solvents and reagents were obtained as follows: tetrahydrofuran and diethyl ether, distillation from sodium and benzophenone; dichloromethane, distillation from CaH_2 ; triethylamine, distillation from CaH_2 . All other solvents were HPLC grade. Column chromatography was performed with Whatman 240–400 mesh silica gel under low pressure of 5–10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

4,4,4-Trichlorobutyraldehyde (8): A mixture of methyl acrylate (2.00 g, 23.2 mmol), NaOH (10.0 g), BnEt_3NCl (0.10 g), chloroform (20.0 g) and water (10.0 g) was vigorously stirred at 0 °C for 2 h. After addition of CH_2Cl_2 and water, the organic phase was separated, washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Distillation of the residue furnished methyl 4,4,4-trichlorobutanoate (1.50 g, 32%) as a colourless liquid. b.p. 80 °C/1 Torr (ref.^[32–34] b.p. 80 °C/0.3 Torr). ^1H NMR (CDCl_3 , 500 MHz): δ = 3.74 (s, 3 H), 3.07 (m, 2 H), 2.82 (m, 2 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 171.9, 98.9, 52.5, 50.3, 31.6 ppm. IR (film): $\tilde{\nu}$ = 1742 (s) cm^{-1} . HRMS (ES, m/z): calcd. $\text{C}_5\text{H}_7\text{Cl}_3\text{NaO}_2$ [$\text{M} + \text{Na}^+$] 226.9409, found 226.9416. A solution of methyl 4,4,4-trichlorobutanoate (1.34 g, 6.54 mmol) in CH_2Cl_2 (80 mL) was cooled to –78 °C. DIBAL (1.0 M in hexanes, 6.54 mL, 6.54 mmol) was added dropwise and the reaction mixture was stirred for 1.5 h at –78 °C. After the reaction had been quenched with aqueous potassium sodium tartrate, the organic layer was dried with Na_2SO_4 and concentrated in vacuo to give **8** (1.09 g, 95%) as a colourless liquid. ^1H NMR (CDCl_3 , 500 MHz): δ = 9.81 (s, 1 H), 3.02 (m, 2 H), 2.97 (m, 2 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 198.4, 98.8, 47.3, 40.9 ppm. IR (film): $\tilde{\nu}$ = 3439 (br. s), 1728 (s) cm^{-1} . HRMS (ES, m/z): calcd. $\text{C}_4\text{H}_5\text{Cl}_3\text{NaO}$ [$\text{M} + \text{Na}^+$] 196.9304, found 196.9295.

(1'S,2'R)-1'-*p*-Tosylaminoindan-2'-yl 4-Methylpentanoate (11): (1S,2R)-1-Aminoindan-2-ol (746 mg, 5.00 mmol) was dissolved in CH_2Cl_2 (50 mL) and the solution was cooled to 0 °C. *p*-Toluenesulfonyl chloride (953 mg, 5.00 mmol) and DMAP (1.22 g, 10.0 mmol) were added, and the mixture was stirred for 1 h at room temperature to generate **10** in situ. 4-Methylvaleric acid (630 μL , 5.00 mmol) and EDCI {*N*-ethyl-*N'*-[3-(dimethylamino)propyl] carbodiimide hydrochloride} (959 mg, 5.00 mmol) were added, and after 2 h of stirring at room temperature, the reaction mixture was successively extracted with saturated aqueous NH_4Cl and NaHCO_3 . Drying of the organic layer with Na_2SO_4 and concentration in vacuo yielded **11** (1.98 g, 99%) as a white solid. M.p. 115–116 °C. $[\alpha]_D^{25}$ = –79.7 (c = 0.74, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ = 7.80 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.27–7.15 (m, 4 H), 5.47 (d, J = 10.4 Hz, 1 H), 5.11 (ddd, J = 4.0, 4.0, 0.8 Hz, 1 H), 4.97 (dd, J = 10.0, 5.2 Hz, 1 H), 3.06 (dd, J = 17.2, 4.8 Hz, 1 H), 2.87 (d, J = 17.2 Hz, 1 H), 2.43 (s, 3 H), 2.13 (dd, J = 8.0, 8.0 Hz, 2 H), 1.46 (m, 1 H), 1.36 (dd, J = 8.1, 8.1 Hz, 2 H), 0.83 (d, J = 6.4 Hz, 3 H), 0.82 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (CHCl_3 , 100 MHz): δ = 173.0, 143.8, 139.8, 138.7, 137.9, 129.9, 128.6, 127.4, 126.9, 125.0, 124.3, 74.6, 59.5, 37.5, 33.4, 32.0, 27.6, 22.2, 21.6 ppm. IR (film): $\tilde{\nu}$ = $\tilde{\nu}$ = 3280 (br. s), 1737

(s) cm^{-1} . HRMS (ES, m/z): calcd. $\text{C}_{22}\text{H}_{27}\text{NNaO}_4\text{S}$ [$\text{M} + \text{Na}^+$] 424.1559, found 424.1575.

(2S,3S,1'S,2'R)-1'-Tosylaminoindan-2'-yl 6,6,6-Trichloro-3-hydroxy-2-isobutylhexanoate (12): TiCl_4 (0.39 mL, 3.56 mmol) was added at 0 °C to a solution of **11** (1.43 g, 3.56 mmol) in CH_2Cl_2 (50 mL). After the mixture had been stirred for 15 min, *i*Pr₂NEt (2.17 mL, 12.5 mmol) was added dropwise at 0 °C and the resulting mixture was stirred for 2 h at room temperature. It was then cooled to –78 °C, and TiCl_4 (0.78 mL, 7.12 mmol) was added in one portion. Subsequently, **8** (0.63 g, 7.12 mmol) in CH_2Cl_2 (2 mL) was added dropwise over a period of 5 min. After the mixture had been stirred for 10 min at –78 °C, the reaction was quenched with saturated aqueous NH_4Cl and the organic phase was dried with Na_2SO_4 . Concentration in vacuo (crude NMR showed 90% *de*) and chromatographic purification (silica, 30% EtOAc in hexanes) yielded **12** (1.85 g, 90%) as a white solid. M.p. 185–188 °C (decomp.). $[\alpha]_D^{25}$ = –14.1 (c = 1.92, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 7.84 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.29–7.19 (m, 4 H), 6.25 (d, J = 10.0 Hz, 1 H), 5.42 (dd, J = 5.0, 5.0 Hz, 1 H), 4.90 (dd, J = 10.0, 5.0 Hz, 1 H), 3.72 (m, 1 H), 3.29 (d, J = 7.0 Hz, 1 H), 3.12 (dd, J = 17.5, 5.0 Hz, 1 H), 2.96 (ddd, J = 14.5, 11.0, 4.5 Hz, 1 H), 2.93 (d, J = 17.0 Hz, 1 H), 2.66 (ddd, J = 15.0, 11.0, 4.5 Hz, 1 H), 2.57 (ddd, J = 15.0, 6.5, 4.5 Hz, 1 H), 2.45 (s, 3 H), 1.95–1.86 (m, 2 H), 1.60 (ddd, J = 13.5, 10.5, 4.5 Hz, 1 H), 1.47 (m, 1 H), 1.22 (ddd, J = 13.5, 9.5, 4.5 Hz, 1 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 173.3, 144.1, 140.3, 138.8, 138.0, 130.3, 128.9, 127.9, 127.6, 125.3, 124.8, 100.2, 75.8, 72.2, 60.1, 52.0, 51.0, 38.4, 37.7, 32.5, 26.7, 23.7, 22.2, 22.0 ppm. IR (film): $\tilde{\nu}$ = 3484 (br. s), 3273 (br. s), 1732 (s) cm^{-1} . HRMS (ES, m/z): calcd. $\text{C}_{26}\text{H}_{32}\text{Cl}_3\text{NNaO}_5\text{S}$ [$\text{M} + \text{Na}^+$] 598.0964, found 598.0969.

(4S,5S)-4-Isobutyl-5-(3',3',3'-trichloroprop-1'-yl)-1,3-oxazolidin-2-one (13): A mixture of **12** (433 mg, 7.51 mmol), $\text{LiOH}\cdot\text{H}_2\text{O}$ (95.0 mg, 2.25 mmol) and H_2O_2 (30%, 153 μL , 4.50 mmol) in THF (10 mL) and water (3 mL) was vigorously stirred for 12 h at 23 °C. In order to obtain a biphasic solution, saturated aqueous NaHCO_3 (20 mL) and diethyl ether (20 mL) were added. The water layer was acidified with concentrated HCl (pH = 2) and extracted with CH_2Cl_2 . The organic layer was dried with Na_2SO_4 , concentrated in vacuo and chromatographically purified (silica, 40% EtOAc in hexanes) to yield (2S,3S)-6,6,6-trichloro-3-hydroxy-2-isobutylhexanoic acid (212 mg, 97%) as a white solid. M.p. 145–147 °C. $[\alpha]_D^{25}$ = –21.7 (c = 1.57, MeOH). ^1H NMR ($[\text{D}_4]\text{MeOH}$, 300 MHz): δ = 4.94 (br. s), 3.77 (ddd, J = 6.9, 2.7, 2.7 Hz, 1 H), 3.00 (m, 1 H), 2.78 (m, 1 H), 2.53 (m, 1 H), 2.03 (m, 1 H), 1.85 (m, 1 H), 1.60 (m, 2 H), 1.25 (m, 1 H), 0.94 (d, J = 1.4 Hz, 3 H), 0.92 (d, J = 1.5 Hz, 3 H) ppm. ^{13}C NMR ($[\text{D}_4]\text{MeOH}$, 75 MHz): δ = 178.1, 101.4, 72.4, 53.0, 52.0, 38.8, 32.7, 27.6, 24.0, 22.0 ppm. IR (film): $\tilde{\nu}$ = 3216 (br. s), 1705 (s) cm^{-1} . HRMS (ES, m/z): calcd. $\text{C}_9\text{H}_{15}\text{Cl}_3\text{NaO}_3$ [$\text{M} + \text{Na}^+$] 298.9984, found 298.9979. A solution of (2S,3S)-6,6,6-trichloro-3-hydroxy-2-isobutylhexanoic acid (135 mg, 4.63 mmol), diphenylphosphoryl azide (0.10 mL, 4.63 mmol) and triethylamine (0.13 mL, 9.26 mmol) in CH_2Cl_2 was heated under reflux for 12 h. After evaporation of solvent, the residue was chromatographically purified (silica, 30% EtOAc in hexanes) to yield **13** (126 mg, 94%) as a colourless oil. $[\alpha]_D^{25}$ = –57.6 (c = 1.63, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ = 6.87 (s, 1 H), 4.22 (m, 1 H), 3.59 (m, 1 H), 3.03 (m, 1 H), 2.78 (m, 1 H), 2.16 (m, 2 H), 1.69 (m, 1 H), 1.55 (m, 1 H), 1.40 (m, 1 H), 0.97 (d, J = 6.0 Hz, 3 H), 0.95 (d, J = 5.8 Hz, 3 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 159.3, 98.9, 81.3, 56.4, 50.8, 44.4, 31.6, 24.9, 23.2, 21.8 ppm. IR (film): $\tilde{\nu}$ = 3266 (br. s), 1755 (s) cm^{-1} . HRMS (ES, m/z): calcd. $\text{C}_{10}\text{H}_{17}\text{Cl}_3\text{NO}_2$ [$\text{M} + \text{H}^+$] 288.0325, found 288.0330.

(4*S*,5*S*)-tert-Butyl 4-Isobutyl-2,2-dimethyl-5-(3',3',3'-trichloropropyl)-1,3-oxazolidine-3-carboxylate (14): A solution of **13** (0.55 g, 1.91 mmol), Boc₂O (0.57 mL, 2.48 mmol), DMAP (0.05 g, 0.38 mmol) and NEt₃ (0.32 mL, 2.29 mmol) in THF (50 mL) was stirred for 3 h at room temperature. NaOH (0.30 g, 7.62 mmol), EtOH (50 mL) and water (50 mL) were added. The resulting mixture was stirred for 5 min at room temperature, quenched with saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The organic layer was dried with Na₂SO₄, concentrated in vacuo and chromatographically purified (silica, 30% EtOAc in hexanes) to yield (1*S*,2*S*)-tert-butyl 5,5,5-trichloro-2-hydroxy-1-isobutylpentylcarbamate (0.63 g, 91%) as a white solid. M.p. 78–82 °C. $[\alpha]_D^{25} = -30.5$ ($c = 1.67$, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): $\delta = 4.74$ (d, $J = 8.7$ Hz, 1 H), 3.58 (br. s, 2 H), 3.05 (d, $J = 4.5$ Hz, 1 H), 2.89 (m, 1 H), 2.77 (m, 1 H), 1.93 (m, 2 H), 1.64 (m, 1 H), 1.40 (m, 1 H), 1.42 (s, 9 H), 1.26 (m, 1 H), 0.92 (d, $J = 6.3$ Hz, 6 H) ppm. ¹³C NMR (CHCl₃, 75 MHz): $\delta = 156.6$, 100.1, 79.7, 73.0, 52.9, 51.8, 40.9, 31.1, 28.3, 24.8, 23.3, 22.0 ppm. IR (film): $\tilde{\nu} = 3431$ (br. s), 1787 (s) cm⁻¹. HRMS (ES, m/z): calcd. C₁₄H₂₆Cl₃NNaO₃ [M + Na⁺] 384.0876, found 384.0885. A solution of (1*S*,2*S*)-tert-butyl 5,5,5-trichloro-2-hydroxy-1-isobutylpentylcarbamate (0.96 g, 2.65 mmol), 2,2-dimethoxypropane (1.63 mL, 13.2 mmol), TsOH·H₂O (0.05 g, 0.26 mmol) and Na₂SO₄ (0.50 g) in CH₂Cl₂ (30 mL) was stirred at room temperature for 15 min. The reaction mixture was extracted with saturated aqueous NaHCO₃, and the organic layer was dried with Na₂SO₄ and concentrated in vacuo to furnish **14** (1.03 g, 97%) as a colourless oil. $[\alpha]_D^{25} = -7.8$ ($c = 2.11$, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): $\delta = 3.90$ (ddd, $J = 10.2$, 3.9, 2.4 Hz, 1 H), 3.77/3.67 (2 br. s, 1 H), 2.95 (ddd, $J = 15.7$, 11.1, 3.6 Hz, 1 H), 2.70 (ddd, $J = 15.9$, 11.7, 4.8 Hz, 1 H), 2.10 (m, 1 H), 1.94 (m, 1 H), 1.65–1.40 (m, 18 H), 0.93 (br. s, 6 H) ppm. ¹³C NMR (CHCl₃, 75 MHz): $\delta = 151.7$, 99.7, 94.4/94.3, 79.9/79.2, 79.1/78.7, 61.1, 51.6, 43.5/42.2, 33.0, 29.1/28.9, 28.5, 28.0/27.7, 25.7, 24.0, 21.4 ppm. IR (film): $\tilde{\nu} = 1702$ (s) cm⁻¹. HRMS (ES, m/z): calcd. C₁₇H₃₀Cl₃NNaO₃ [M + Na⁺] 424.1189, found 424.1195.

(4*S*,5*S*)-tert-Butyl 4-Isobutyl-2,2-dimethyl-5-prop-2'-ynyl-1,3-oxazolidine-3-carboxylate (15) from 22: A solution of TsCl (8.00 g, 42.0 mmol) and NaN₃ (2.73 g, 42.0 mmol) in acetone (120 mL) and H₂O (120 mL) was stirred at 0 °C for 2 h. Acetone was evaporated, the reaction mixture was extracted with diethyl ether, and the organic phase was dried with Na₂SO₄. Evaporation of solvent gave tosyl azide (8.07 g, 97%) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz): $\delta = 7.75$ (d, $J = 8.1$ Hz, 2 H), 7.33 (d, $J = 8.1$ Hz, 2 H), 2.39 (s, 3 H) ppm. ¹³C NMR (CHCl₃, 75 MHz): $\delta = 146.3$, 135.4, 130.3, 127.5, 21.7 ppm. IR (film): $\tilde{\nu} = 2129$ (s), 1171 (s) cm⁻¹. A solution of NaH (60% dispersion in mineral oil, 0.99 g, 41.5 mmol) in THF (100 mL) was cooled to 0 °C. Dimethyl (2-oxopropyl)phosphonate (6.26 g, 37.7 mmol) in THF (100 mL) was added dropwise, and the solution was stirred at 0 °C for 1 h. Tosyl azide (8.18 g, 41.5 mmol) was then added in one portion and the resulting mixture was stirred at 0 °C for 10 min. The reaction mixture was quickly passed through a short column (silica, EtOAc) to give dimethyl (1-diazo-2-oxopropyl)phosphonate (6.95 g, 96%) as a colourless oil. Spectroscopic and analytical data are in agreement with those reported.^[48] ¹H NMR (CDCl₃, 300 MHz): $\delta = 3.75$ (s, 3 H), 3.71 (s, 3 H), 2.15 (s, 3 H) ppm. ¹³C NMR (CHCl₃, 75 MHz): $\delta = 189.7$, 115.6, 53.6, 53.5, 27.1 ppm. IR (film): $\tilde{\nu} = 2124$ (s), 1659 (s), 1026 (s) cm⁻¹. A solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (4.79 g, 24.9 mmol), **22** (3.39 g, 11.3 mmol) and Cs₂CO₃ (11.1 g, 34.0 mmol) in *i*PrOH (150 mL) was stirred at 0 °C for 1 h and then at room temperature for a period of 11 h. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with diethyl ether, and the organic phase was dried with

Na₂SO₄. Evaporation of solvent and chromatographic purification (silica, 10% EtOAc in hexanes) yielded **15** (3.24 g, 97%) as a colourless oil. $[\alpha]_D^{25} = +44.3$ ($c = 3.79$, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): $\delta = 3.94$ (td, $J = 6.7$, 1.6 Hz, 1 H), 3.89/3.77 (2 br. s, 1 H), 2.40 (m, 2 H), 1.98 (t, $^4J = 2.7$ Hz, 1 H), 1.53–1.37 (m, 9 H), 1.40 (s, 9 H), 0.88 (d, $J = 6.4$ Hz, 6 H) ppm. ¹³C NMR (CHCl₃, 125 MHz): $\delta = 152.0$, 94.9/94.1, 80.6/80.0, 80.3, 79.5/78.9, 70.8, 60.0, 43.6/42.4, 29.6/28.8, 28.8, 28.5/28.2, 26.2, 25.6, 24.4, 21.5 ppm. IR (film): $\tilde{\nu} = 2121$ (w), 1700 (s) cm⁻¹. LRMS (FAB): $m/z = 296.2$. HRMS (CI, m/z): calcd. C₁₇H₃₀NO₃ [M + H⁺] 296.2226, found 296.2213.

(4*S*,5*S*)-tert-Butyl 5-(3,3-Dichloroprop-2-enyl)-4-isobutyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (16): *n*-Butyllithium (2.5 M in hexanes, 79.2 μ L, 198 μ mol) was added dropwise at –78 °C to a solution of **14** (10.0 mg, 24.8 μ mol) in THF (4 mL) and the mixture was stirred at –78 °C for a further 10 min. The mixture was quenched with saturated aqueous NH₄Cl, diethyl ether was added, and the organic phase was dried with Na₂SO₄. Evaporation of solvent yielded **16** (8.0 mg, 88%) as a colourless film. $[\alpha]_D^{25} = -9.5$ ($c = 0.59$, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): $\delta = 5.85$ (t, $J = 5.7$ Hz, 1 H), 3.87 (ddd, $J = 9.7$, 4.0, 2.5 Hz, 1 H), 3.76/3.64 (2 br. s, 1 H), 2.42 (m, 1 H), 2.26 (m, 1 H), 1.90 (m, 1 H), 1.78 (m, 1 H), 1.65–1.44 (m, 16 H), 0.94 (d, $J = 6.3$ Hz, 6 H) ppm. ¹³C NMR (CHCl₃, 125 MHz): $\delta = 152.1$, 127.6, 94.7/94.5, 80.2/79.6, 73.7, 61.5, 44.0/42.6, 40.3, 32.3/29.5, 28.9, 28.4/28.1, 26.1, 24.4, 21.8 ppm. IR (film): $\tilde{\nu} = 1700$ (s) cm⁻¹.

(4*S*,5*S*)-tert-Butyl 4-Isobutyl-5-(3'-methoxycarbonylprop-2'-ynyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (17): From **14**: *n*-Butyllithium (2.5 M in hexanes, 59.4 μ L, 149 μ mol) was added dropwise at –78 °C to a solution of **14** (40.0 mg, 99.3 μ mol) in THF (3 mL). After the mixture had been stirred for 10 min at –78 °C, *N,N,N',N'*-tetramethylethylenediamine (50.0 μ L, 298 μ mol) and *n*-butyllithium (119 μ L, 298 μ L) were added successively, and the resulting mixture was stirred for another 10 min. Methyl chloroformate (23.0 μ L, 298 μ mol) was added in one portion, and the reaction mixture was allowed to warm to room temperature over a period of 10 min. The reaction was quenched with saturated aqueous NH₄Cl, diethyl ether was added, and the organic phase was dried with Na₂SO₄. Evaporation of solvent yielded **17** (26 mg, 85%) as a white solid. From **15**: *n*-Butyllithium (2.0 M in hexanes, 4.10 mL, 8.12 mmol) was added at –78 °C to a solution of **15** (1.60 g, 5.42 mmol) in THF (150 mL), and the solution was stirred for 10 min. Methyl chloroformate (1.26 mL, 16.3 mmol) was added in one portion, and the reaction mixture was allowed to warm to room temperature over a period of 10 min. The reaction was quenched with saturated aqueous NH₄Cl, diethyl ether was added, and the organic phase was dried with Na₂SO₄. Evaporation of solvent yielded **17** (1.91 g, 99%) as a white solid. M.p. 65 °C. $[\alpha]_D^{25} = +43.2$ ($c = 2.70$, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): $\delta = 4.07$ (t, $J = 6.3$ Hz, 1 H), 3.90/3.82 (2 br. s, 1 H), 3.75 (s, 3 H), 2.62 (m, 2 H), 1.53–1.40 (m, 9 H), 1.48 (s, 9 H), 0.95 (d, $J = 6.2$ Hz, 6 H) ppm. ¹³C NMR (CHCl₃, 100 MHz): $\delta = 153.8$, 151.6, 94.9/94.2, 85.0, 80.0, 78.3/77.5, 74.5, 60.5, 52.6, 43.2/42.0, 29.3/28.6, 28.5, 28.4/27.8, 26.1, 25.6, 24.0, 21.1 ppm. IR (film): $\tilde{\nu} = 1716$ (s), 1700 (s) cm⁻¹; LRMS (CI): $m/z = 354$, 254. HRMS (FAB, m/z): calcd. C₁₉H₃₁NNaO₅ [M + Na⁺] 376.2100, found 376.2102.

(1*S*,2*S*)-tert-Butyl (2-Hydroxy-1-isobutylpent-4-enyl)carbamate (19): SnCl₄ (1.0 M in CH₂Cl₂, 102 mL, 102 mmol) was added at –78 °C to a solution of *N*-Boc-L-leucinal (11.0 g, 51.0 mmol) in CH₂Cl₂ (300 mL) and the reaction mixture was stirred for 10 min. Allyltributyltin (25.0 g, 76.0 mmol) was then added dropwise, and the reaction mixture was stirred at –78 °C for 1 h. The reaction

was quenched with saturated aqueous NH_4Cl , and the organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in MeOH (300 mL), NaBH_4 (3.82 g, 0.10 mol) was added in one portion, and the resulting mixture was vigorously stirred for 2 min. After quenching and extraction with saturated aqueous NaHCO_3 , the organic phase was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (silica, 20% EtOAc in hexanes) to give **19** (11.9 g, 90%) as a colourless oil and the minor diastereomer (0.50 g, 4%). **Major Diastereomer:** $[\alpha]_D^{25} = -29.7$ ($c = 3.30$, MeOH). ^1H NMR (CDCl_3 , 400 MHz): $\delta = 5.83$ (m, 1 H), 5.15 (m, 2 H), 4.70 (d, $J = 9.5$ Hz, 1 H), 3.60 (m, 2 H), 2.31–2.16 (m, 3 H), 1.64 (m, 1 H), 1.48 (m, 1 H), 1.42 (s, 9 H), 1.30 (m, 1 H), 0.92 (d, $J = 2.2$ Hz, 3 H), 0.90 (s, $J = 2.2$ Hz, 3 H) ppm. ^{13}C NMR (CHCl_3 , 100 MHz): $\delta = 156.2$, 134.7, 118.2, 79.1, 72.8, 52.0, 41.8, 39.1, 28.4, 24.8, 23.2, 22.2 ppm. IR (film): $\tilde{\nu} = 3436$ (br. s), 1688 (s) cm^{-1} ; LRMS (CI): $m/z = 258.3$, 202.1. HRMS (CI, m/z): calcd. $\text{C}_{14}\text{H}_{28}\text{NO}_3$ [$\text{M} + \text{H}^+$] 258.2069, found 258.2067. **Minor Diastereomer:** M.p. 101 °C. $[\alpha]_D^{25} = -13.9$ ($c = 0.36$, MeOH). $[\alpha]_D^{25} = -32.6$ ($c = 4.54$, CH_2Cl_2). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 5.86$ (m, 1 H), 5.14 (m, 2 H), 4.67 (d, $J = 7.8$ Hz, 1 H), 3.69 (br. s, 2 H), 2.68 (br. s, 1 H), 2.24–2.16 (m, 2 H), 1.65 (m, 1 H), 1.45 (s, 9 H), 1.36–1.29 (m, 2 H), 0.95 (d, $J = 6.7$ Hz, 3 H), 0.92 (s, $J = 7.2$ Hz, 3 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): $\delta = 156.8$, 135.4, 118.2, 79.9, 74.3, 53.5, 38.8, 38.4, 28.8, 25.2, 24.1, 22.0 ppm. IR (film): $\tilde{\nu} = 1707$ (s), 1503 (s) cm^{-1} .

(1S,2R)-tert-Butyl (2-Hydroxy-1-isobutylpent-4-ynyl)carbamate (20): Zinc (46.0 mg, 0.70 mmol) was added portionwise at 0 °C, over a period of 5 min, to a solution of **18** (50.0 mg, 0.23 mmol) and propargyl bromide (80 w% in toluene, 37.5 mg, 0.26 mmol) in diethyl ether (3 mL) and DMF (3 mL). The reaction mixture was allowed to warm to room temperature, stirred for a further 12 h and filtered through Celite®, and the filtrate was concentrated in vacuo. The residue was chromatographically purified (silica, 30% EtOAc in hexanes) to give **20** (43.0 mg, 67%) as a colourless oil. $[\alpha]_D^{25} = -15.1$ ($c = 0.08$, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): $\delta = 4.60$ (d, $J = 9.0$ Hz, 1 H), 3.60 (m, 2 H), 2.39 (dd, 2 H, $J = 6.2$, $^4J = 2.5$ Hz), 2.36 (br. s, 1 H), 2.05 (t, $^4J = 2.5$ Hz, 1 H), 1.67 (m, 1 H), 1.48 (s, 9 H), 1.34 (m, 2 H), 0.94 (d, $J = 6.6$ Hz, 3 H), 0.91 (d, $J = 6.6$ Hz, 3 H) ppm. ^{13}C NMR (CHCl_3 , 100 MHz): $\delta = 156.6$, 80.9, 79.8, 73.1, 70.7, 53.1, 38.8, 28.3, 24.8, 23.6, 23.4, 21.6 ppm. IR (film): $\tilde{\nu} = 1680$ (s), 1530 (s) cm^{-1} . HRMS (CI, m/z): calcd. $\text{C}_{14}\text{H}_{25}\text{NNaO}_3$ [$\text{M} + \text{H}^+$] 278.1732, found 278.1725.

(4S,5R)-tert-Butyl 4-Isobutyl-2,2-dimethyl-5-prop-2'-ynyl-1,3-oxazolidine-3-carboxylate (21): A mixture of **20** (15.0 mg, 58.0 μmol), 2,2-dimethoxypropane (72.0 μL , 0.58 mmol), $\text{TsOH} \cdot \text{H}_2\text{O}$ (1.7 mg, 10.0 μmol) and Na_2SO_4 (50.0 mg) in CH_2Cl_2 (2 mL) was stirred for 1 h at room temperature. After the reaction mixture had been quenched and extracted with saturated aqueous NaHCO_3 , the organic layer was dried with Na_2SO_4 and concentrated in vacuo to give **21** (17.0 mg, 98%) as a colourless oil. $[\alpha]_D^{25} = +17.9$ ($c = 0.04$, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): $\delta = 4.20$ –3.80 (m, 2 H), 2.58–2.35 (m, 2 H), 2.02 (s, 1 H), 1.73 (m, 1 H), 1.66–1.46 (m, 8 H), 1.47 (s, 9 H), 0.95 (d, $J = 6.2$ Hz, 3 H), 0.94 (d, $J = 6.2$ Hz, 3 H) ppm. IR (film): $\tilde{\nu} = 1685$ (s) cm^{-1} .

(4S,5S)-tert-Butyl 4-Isobutyl-2,2-dimethyl-5-(2'-oxoethyl)-1,3-oxazolidine-3-carboxylate (22): A solution of **19** (2.00 g, 7.77 mmol), 2,2-dimethoxypropane (19.1 mL, 155 mmol), $\text{TsOH} \cdot \text{H}_2\text{O}$ (150 mg, 0.77 mmol) and Na_2SO_4 (1.00 g) in CH_2Cl_2 (40 mL) was stirred for 1 h at room temperature. After the reaction mixture had been quenched and extracted with saturated aqueous NaHCO_3 , the organic layer was dried with Na_2SO_4 and concentrated in vacuo to give (4S,5S)-tert-butyl 5-allyl-4-isobutyl-2,2-dimethyl-1,3-oxazolid-

ine-3-carboxylate (2.30 g, 99%) as a colourless oil. $[\alpha]_D^{25} = +6.2$ ($c = 4.49$, CH_2Cl_2). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 5.80$ (m, 1 H), 5.13 (m, 2 H), 3.90 (t, $J = 6.4$ Hz, 1 H), 3.79/3.68 (2 br. s, 1 H), 2.42 (m, 1 H), 2.32 (m, 1 H), 1.62–1.45 (m, 9 H), 1.49 (s, 9 H), 0.94 (d, $J = 5.6$ Hz, 6 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): $\delta = 152.2$, 134.6, 118.2, 94.5/93.8, 80.9/79.9, 80.3, 60.4, 43.9/42.6, 40.9/40.7, 29.5/28.8, 28.9, 28.4/28.1, 25.7, 24.4, 21.7 ppm. IR (film): $\tilde{\nu} = 1701$ (s), 1177 (s) cm^{-1} ; LRMS (CI): $m/z = 298.2$, 198.3. HRMS (CI, m/z): calcd. $\text{C}_{17}\text{H}_{32}\text{NO}_3$ [$\text{M} + \text{H}^+$] 298.2382, found 298.2370. A solution of (4S,5S)-tert-butyl 5-allyl-4-isobutyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2.52 g, 8.46 mmol) in CH_2Cl_2 (250 mL) was cooled to -78 °C. Ozone was passed through the solution until the blue colour persisted. Oxygen and nitrogen were successively passed through the solution for at least 10 min each. PPh_3 (2.33 g, 8.88 mmol) was added portionwise under N_2 , and the reaction mixture was allowed to warm to room temperature over a period of 1 h. Evaporation of solvent and chromatographic purification (silica, 10% EtOAc in hexanes) of the residue yielded **22** (2.46 g, 97%) as a colourless oil. $[\alpha]_D^{25} = +8.3$ ($c = 5.04$, CH_2Cl_2). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 9.82$ (s, $J = 1.2$ Hz, 1 H), 4.43 (t, $J = 5.8$ Hz, 1 H), 3.81/3.67 (2 br. s, 1 H), 2.81 (br, 1 H), 2.71 (ddd, $J = 16.8$, 6.1, 1.2 Hz, 1 H), 1.62–1.45 (m, 9 H), 1.49 (s, 9 H), 0.96 (d, $J = 6.4$ Hz, 6 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): $\delta = 200.6$, 152.1, 94.9/94.3, 80.3, 75.7/75.3, 61.4, 50.1, 43.9/42.6, 29.5/28.9, 28.9, 28.4/28.0, 25.9, 23.1, 21.7 ppm. IR (film): $\tilde{\nu} = 3365$ (br. s), 1726 (m), 1698 (s) cm^{-1} . LRMS (CI): $m/z = 300$, 216. HRMS (CI, m/z): calcd. $\text{C}_{16}\text{H}_{30}\text{NO}_4$ [$\text{M} + \text{H}^+$] 300.2175, found 300.2182.

(4S,5S)-tert-Butyl 4-Isobutyl-5-(3-methoxy-2-methoxycarbonylbenzyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (24): A mixture of **17** (1.00 g, 2.83 mmol), 1-methoxy-1,3-cyclobutadiene (65% tech., 4.90 mL, 28.3 mmol) and toluene (5 mL) was vigorously stirred in a sealed tube at 175 °C for 3 d. Chromatographic purification (silica, 10% EtOAc in hexanes) of the reaction mixture furnished **24** (0.94 g, 76%) as a colourless oil. $[\alpha]_D^{25} = +4.1$ ($c = 1.47$, CH_2Cl_2). ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.30$ (dd, $J = 8.3$, 8.0 Hz, 1 H), 6.89 (d, $J = 8.0$ Hz, 1 H), 6.80 (d, $J = 8.3$ Hz, 1 H), 4.09 (t, $J = 6.5$ Hz, 1 H), 3.90/3.82 (2 br. s, 1 H), 3.90 (s, 3 H), 3.82 (s, 3 H), 2.93 (dd, $J = 13.6$, 6.5 Hz, 1 H), 2.75 (dd, $J = 13.6$, 6.5 Hz, 1 H), 1.68–1.63 (m, 3 H), 1.48–1.41 (m, 6 H), 1.46 (s, 9 H), 0.82 (d, $J = 6.6$ Hz, 6 H) ppm. ^{13}C NMR (CHCl_3 , 100 MHz): $\delta = 168.9$, 157.0, 152.2, 136.7, 130.8, 124.6, 123.0, 109.7, 94.8/94.1, 81.7/81.0, 80.3/80.0, 60.5/60.2, 56.4, 52.7, 43.7/42.3, 40.2, 30.1/29.9, 28.9, 28.8/28.3, 25.8, 24.4, 21.1 ppm. IR (film): $\tilde{\nu} = 1733$ (s), 1696 (s) cm^{-1} . LRMS (FAB): $m/z = 436$, 336. HRMS (FAB, m/z): calcd. $\text{C}_{24}\text{H}_{37}\text{NNaO}_6$ [$\text{M} + \text{Na}^+$] 458.2519, found 458.2521.

(1S,3'S)-tert-Butyl [1-(8'-Methoxy-1'-oxoisochroman-3'-yl)-3-methylbutyl]carbamate (2): A mixture of **24** (560 mg, 1.28 mmol), *p*-toluenesulfonic acid monohydrate (24.0 mg, 0.13 mmol), water (30 μL) and CH_2Cl_2 (8 mL) was stirred for 20 min at ambient temperature. The reaction mixture was quenched and extracted with saturated aqueous NaHCO_3 , and the organic layer was dried with Na_2SO_4 and concentrated in vacuo. Chromatographic purification (silica, 20% EtOAc in hexanes) gave **2** (450 g, 97%) as a white solid. M.p. 138–145 °C {ref.^[19] m.p. 143.5–144.5 °C}. $[\alpha]_D^{25} = -151.7$ ($c = 1.32$, CHCl_3) (ref.^[19] $[\alpha]_D^{25} = -153.8$ ($c = 0.86$, CHCl_3)). $[\alpha]_D^{25} = -101.5$ ($c = 2.10$, MeOH). ^1H NMR (CDCl_3 , 300 MHz): $\delta = 7.42$ (dd, $J = 8.4$, 8.4 Hz, 1 H), 6.88 (d, $J = 8.4$ Hz, 1 H), 6.80 (d, $J = 8.4$ Hz, 1 H), 4.81 (d, $J = 10.2$ Hz, 1 H), 4.35 (d, $J = 12.6$ Hz, 1 H), 3.92 (s, 3 H), 3.87 (d, $J = 10.2$ Hz, 1 H), 3.06 (dd, $J = 15.9$, 12.9 Hz, 1 H), 2.74 (dd, $J = 16.2$, 1.8 Hz, 1 H), 1.75–1.60 (m, 2 H), 1.41 (s, 9 H), 1.39 (m, 1 H), 0.90 (d, $J = 6.6$ Hz, 6 H) ppm.

^{13}C NMR (CHCl_3 , 75 MHz): δ = 162.4, 161.0, 155.8, 142.2, 134.5, 119.4, 113.4, 110.6, 79.6, 79.4, 56.1, 50.4, 41.0, 31.7, 28.2, 24.6, 22.8, 22.0 ppm. IR (film): $\tilde{\nu}$ = 3344 (br. s), 1726 (s), 1694 (s) cm^{-1} . LRMS (FAB): m/z = 386. HRMS (FAB, m/z): calcd. $\text{C}_{20}\text{H}_{29}\text{NNaO}_5$ [$\text{M} + \text{Na}^+$] 386.1943, found 386.1964.

(1'S,2'R)-1'-*p*-Tosylaminoindan-2'-yl Pent-4-enoate (25): (1*S*,2*R*)-1-Aminoindan-2-ol (1.69 g, 11.3 mmol) was dissolved in CH_2Cl_2 (50 mL) and the solution was cooled to 0 °C. *p*-Toluenesulfonyl chloride (2.15 g, 11.3 mmol) and DMAP (2.76 g, 11.3 mmol) were added and the mixture was stirred for 1 h at room temperature to generate **10** in situ. 4-Pentenoic acid (1.13 g, 11.3 mmol), EDCI (2.16 g, 11.3 mmol) and DMAP (1.38 g, 11.3 mmol) were added, and the mixture was stirred for 4 h at room temperature. The reaction mixture was extracted with saturated aqueous NH_4Cl and NaHCO_3 . The organic layer was dried with Na_2SO_4 and concentrated in vacuo to yield **25** (4.31 g, 99%) as a white solid. M.p. 120–121 °C. $[\alpha]_D^{25}$ = -76.0 (c = 1.59, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ = 7.81 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.26–7.22 (m, 3 H), 7.17 (m, 1 H), 5.72 (m, 1 H), 5.38 (d, J = 10.1 Hz, 1 H), 5.14 (ddd, J = 5.2, 5.2, 1.0 Hz, 1 H), 4.96 (m, 3 H), 3.07 (dd, J = 17.3, 5.0 Hz, 1 H), 2.88 (d, J = 17.3 Hz, 1 H), 2.44 (s, 3 H), 2.23 (m, 4 H) ppm. ^{13}C NMR (CHCl_3 , 100 MHz): δ = 171.9, 143.8, 139.7, 138.6, 137.9, 136.4, 129.9, 128.6, 127.4, 127.0, 125.0, 124.3, 115.7, 74.8, 59.5, 37.5, 33.2, 28.6, 21.6 ppm. IR (film): $\tilde{\nu}$ = 3283 (br. s), 1738 (s) cm^{-1} . LRMS (FAB, m/z): 408. HRMS (FAB, m/z): calcd. $\text{C}_{21}\text{H}_{23}\text{NNaO}_4\text{S}$ [$\text{M} + \text{Na}^+$] 408.1246, found 408.1256.

(2*S*,1'*S*,1''*S*,2''*R*)-1''-*p*-Tosylaminoindan-2''-yl 2-(2'-Benzyloxy-1'-hydroxyethyl)pent-4-enoate (26): TiCl_4 (1.43 mL, 13.0 mmol) was added at 0 °C to a solution of **25** (5.02 g, 13.0 mmol) in CH_2Cl_2 (150 mL). After the mixture had been stirred for 15 min, $i\text{Pr}_2\text{NEt}$ (8.61 mL, 49.4 mmol) was added dropwise at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. It was then cooled to -78 °C, and TiCl_4 (2.85 mL, 26.0 mmol) was added in one portion. Subsequently, benzyloxyacetaldehyde (1.83 mL, 26.0 mmol) was added dropwise over a period of 4 min. After stirring for 1 h at -78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and the organic layer was dried with Na_2SO_4 . Concentration in vacuo (crude NMR showed 98% *de*) and chromatographic purification (silica, 20% EtOAc in hexanes) yielded **26** (6.76 g, 97%) as a white solid. M.p. 165–167 °C. $[\alpha]_D^{25}$ = -61.2 (c = 0.85, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.81 (d, J = 8.1 Hz, 2 H), 7.36–7.21 (m, 10 H), 7.14 (m, 1 H), 5.95 (d, J = 9.9 Hz, 1 H), 5.65 (dddd, 1 H, J = 16.8, 10.2, 6.6, 6.6 Hz), 5.30 (dd, J = 4.5, 4.4 Hz, 1 H), 4.99 (d, J = 10.2 Hz, 1 H), 4.90 (d, J = 16.2 Hz, 1 H), 4.89 (dd, J = 9.5, 4.8 Hz, 1 H), 4.42 (s, 2 H), 4.01 (br. s, 1 H), 3.45 (dd, J = 9.9, 4.2 Hz, 1 H), 3.37 (dd, J = 9.6, 6.9 Hz, 1 H), 3.03 (dd, J = 17.1, 4.2 Hz, 1 H), 2.95 (br. s, 1 H), 2.84 (d, J = 17.1 Hz, 1 H), 2.60 (ddd, J = 9.3, 5.4, 5.2 Hz, 1 H), 2.43 (s, 3 H), 2.27 (m, 2 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 172.3, 143.5, 139.9, 138.4, 137.9, 137.5, 135.2, 129.8, 128.4, 127.8, 127.3, 127.0, 124.7, 124.2, 117.2, 75.7, 73.3, 71.5, 70.4, 59.5, 48.3, 37.1, 30.8, 21.5 ppm. IR (film): $\tilde{\nu}$ = 3497 (br. s), 3286 (br. s), 1731 (s), 1449 (s) cm^{-1} . HRMS (FAB, m/z): calcd. $\text{C}_{30}\text{H}_{34}\text{NO}_6\text{S}$ [$\text{M} + \text{H}^+$] 536.2107, found 536.2123.

(4*S*,5*S*)-4-Allyl-5-benzyloxymethyl-1,3-oxazolidin-2-one (27): A mixture of **26** (30%, 8.35 g, 15.6 mmol), hydrogen peroxide (10.6 mL, 9.34 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (1.96 g, 4.67 mmol) in THF (90 mL), ethanol (50 mL) and water (30 mL) was stirred for 3 h at room temperature and subsequently quenched with aqueous Na_2SO_3 (1.0 M). Aqueous NaOH was added (pH = 12), organic solvents were removed in vacuo, diethyl ether was added, and the

resulting mixture was acidified with concentrated HCl (pH = 2). The organic layer was then dried with Na_2SO_4 , concentrated in vacuo and chromatographically purified (silica, 50% EtOAc in hexanes) to furnish (2*S*,1'*S*)-2-(2'-benzyloxy-1'-hydroxyethyl)pent-4-enoic acid (3.74 g, 96%) as a white solid. M.p. 42 °C. $[\alpha]_D^{25}$ = -5.9 (c = 4.10, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.38–7.26 (m, 5 H), 5.80 (dddd, 1 H, J = 17.1, 10.2, 6.9, 6.6 Hz), 5.10 (d, J = 18.3 Hz, 1 H), 5.05 (d, J = 11.4 Hz, 1 H), 4.55 (s, 2 H), 4.06 (br. s, 1 H), 3.54 (m, 2 H), 2.72 (m, 1 H), 2.47 (m, 2 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 178.8, 137.4, 134.8, 128.4, 127.9, 127.7, 117.2, 73.3, 71.6, 70.1, 48.0, 32.0 ppm. IR (film): $\tilde{\nu}$ = 3426 (br. s), 1710 (s) cm^{-1} . LRMS (FAB, m/z): 251. HRMS (FAB, m/z): calcd. $\text{C}_{14}\text{H}_{19}\text{O}_4$ [$\text{M} + \text{H}^+$] 251.1283, found 251.1289. A solution of (2*S*,1'*S*)-2-(2'-benzyloxy-1'-hydroxyethyl)pent-4-enoic acid (3.50 g, 14.0 mmol), diphenylphosphoryl azide (4.52 mL, 21.0 mmol) and triethylamine (2.92 mL, 21.0 mmol) in CH_2Cl_2 (150 mL) was stirred under reflux for 12 h. Removal of solvents and chromatographic purification (silica, 50% EtOAc in hexanes) yielded **27** (3.18 g, 92%) as a white solid. M.p. 43–47 °C. $[\alpha]_D^{25}$ = -22.7 (c = 6.11, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.37–7.25 (m, 5 H), 5.70 (dddd, 1 H, J = 17.2, 10.3, 6.7, 6.4 Hz), 5.58 (br. s, 1 H), 5.17 (d, J = 9.9 Hz, 1 H), 5.14 (d, J = 17.1 Hz, 1 H), 4.77 (ddd, J = 7.8, 6.2, 6.0 Hz, 1 H), 4.57 (s, 2 H), 3.90 (ddd, J = 10.2, 7.8, 3.9 Hz, 1 H), 3.71 (d, J = 6.3 Hz, 2 H), 2.41 (dddd, 1 H, J = 14.1, 3.9, 3.9, 4J = 1.5 Hz), 2.20 (m, 1 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 158.4, 137.2, 133.0, 128.4, 127.9, 127.8, 119.3, 77.1, 73.7, 76.1, 53.7, 34.3 ppm. IR (film): $\tilde{\nu}$ = 3279 (br. s), 1754 (s) cm^{-1} . LRMS (FAB, m/z): 248. HRMS (FAB, m/z): calcd. $\text{C}_{14}\text{H}_{18}\text{O}_3\text{N}$ [$\text{M} + \text{H}^+$] 248.1287, found 248.1277.

(1*S*,1'*S*)-tert-Butyl [1-(2'-Benzyloxy-1'-hydroxyethyl)but-3-enyl]carbamate (28): A solution of **27** (3.00 g, 12.1 mmol), di-*tert*-butyl dicarbonate (3.62 mL, 15.8 mmol), triethylamine (2.03 mL, 14.6 mmol) and 4-(dimethylamino)pyridine (0.30 g, 2.43 mmol) in THF (100 mL) was stirred for 2 h at room temperature. Ethanol (100 mL), water (100 mL) and sodium hydroxide (2.00 g, 50.0 mmol) were added, and the resulting mixture was stirred for 5 min at room temperature. Organic solvents were removed, CH_2Cl_2 (200 mL) was added, and the aqueous phase was acidified (pH = 3) with concentrated HCl. The organic layer was dried with Na_2SO_4 and concentrated in vacuo to yield **28** (3.75 g, 96%) as a white solid. M.p. 50 °C. $[\alpha]_D^{25}$ = $+4.07$ (c = 2.00, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.38–7.26 (m, 5 H), 5.77 (dddd, 1 H, J = 16.9, 10.2, 6.7, 6.2 Hz), 5.11–5.05 (m, 2 H), 4.82 (br. d, J = 7.5 Hz, 1 H), 4.55 (s, 2 H), 3.77 (br. m, 2 H), 3.60–3.49 (m, 2 H), 2.69 (br. s, 1 H), 2.30 (m, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 156.0, 137.7, 134.4, 128.4, 127.8, 127.7, 117.7, 79.4, 73.5, 71.9, 71.7, 52.5, 35.1, 28.3 ppm. IR (film): $\tilde{\nu}$ = 3353 (br. s), 1684 (s), 1526 (s) cm^{-1} . LRMS (FAB, m/z): 322. HRMS (FAB, m/z): calcd. $\text{C}_{18}\text{H}_{28}\text{O}_4\text{N}$ [$\text{M} + \text{H}^+$] 322.2018, found 322.2027.

(4*S*,5*S*)-tert-Butyl 4-Allyl-5-benzyloxymethyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (6): A solution of **28** (3.50 g, 10.9 mmol), 2,2-dimethoxypropane (6.70 mL, 55.0 mmol), $\text{TsOH}\cdot\text{H}_2\text{O}$ (210 mg, 1.09 mmol) and Na_2SO_4 (1.00 g) in CH_2Cl_2 (100 mL) was stirred for 1 h at room temperature. Extraction of the reaction mixture with saturated aqueous NaHCO_3 , drying with Na_2SO_4 and concentration in vacuo furnished **6** (3.62 g, 92%) as a colourless oil. $[\alpha]_D^{25}$ = -17.0 (c = 6.48, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 7.37–7.29 (m, 5 H), 5.80 (m, 1 H), 5.03 (m, 2 H), 4.64 (dd, J = 12.1, 5.3 Hz, 1 H), 4.52 (d, J = 12.1 Hz, 1 H), 4.31 (dd, J = 11.2, 5.5 Hz, 1 H), 4.11 (dd, J = 11.2, 5.5 Hz, 1 H), 3.98 (dd, J = 11.2, 5.4 Hz, 1 H), 3.63 (m, 2 H), 2.38 (m, 1 H), 2.29 (m, 1 H), 1.63/1.59 (2 s, 3 H), 1.57/1.54 (2 s, 3 H), 1.49/1.47 (2 s, 9 H) ppm.

^{13}C NMR (CHCl_3 , 125 MHz): δ = 152.5/152.0, 138.2/138.1, 135.8, 128.8, 128.4/128.2, 128.2/128.1, 117.2/117.0, 93.8/93.3, 80.4/80.0, 75.9, 74.0/73.9, 68.6/68.3, 58.4, 35.2/34.8, 28.9/28.8, 28.1/27.3, 25.4/24.1 ppm. IR (film): $\tilde{\nu}$ = 1694 (s) cm^{-1} . LRMS (FAB, m/z): 362. HRMS (FAB, m/z): calcd. $\text{C}_{21}\text{H}_{32}\text{O}_4\text{N}$ [$\text{M} + \text{H}^+$] 362.2331, found 362.2345.

(4*S*,5*S*)-tert-Butyl 4-Allyl-5-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (29): A solution of **6** (3.62 g, 10.0 mmol) in THF (25 mL) was added at -78°C to a solution of lithium (236 mg, 34.1 mmol) in ammonia (50 mL). The resulting reaction mixture was stirred for 5 min at -78°C , quenched with solid NH_4Cl and allowed to warm to room temperature. Extraction with diethyl ether and removal of solvent yielded (4*S*,5*S*)-tert-butyl 4-allyl-5-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2.57 g, 95%) as a colourless oil. $[\alpha]_{\text{D}}^{23} = -1.54$ (c = 3.25, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz): δ = 5.79 (m, 1 H), 5.08 (d, J = 17.1 Hz, 1 H), 5.03 (d, J = 10.2 Hz, 1 H), 4.19 (dd, J = 10.2, 5.4 Hz, 1 H), 4.06/3.94 (2 s, 1 H), 3.83–3.70 (m, 2 H), 2.35 (m, 1 H), 2.26 (br. s, 1 H), 2.08 (m, 1 H), 1.58/1.55 (2 s, 3 H), 1.52/1.51 (2 s, 3 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 152.5/152.2, 135.2, 117.1, 93.2/92.8, 80.0/79.7, 77.1, 60.9, 57.8, 34.7/34.1, 28.3, 27.7/26.9, 24.8/23.5 ppm. IR (film): $\tilde{\nu}$ = 3454 (br. s), 1696 (s) cm^{-1} . LRMS (FAB, m/z): 272. HRMS (FAB, m/z): calcd. $\text{C}_{14}\text{H}_{26}\text{O}_4\text{N}$ [$\text{M} + \text{H}^+$] 272.1862, found 272.1865. DMSO (3.92 mL, 55.3 mmol) was added at -78°C to a solution of oxalyl chloride (2.41 mL, 27.6 mmol) in CH_2Cl_2 (100 mL). The resulting reaction mixture was stirred for 30 min at -78°C , and a solution of (4*S*,5*S*)-tert-butyl 4-allyl-5-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2.50 g, 9.21 mmol) in CH_2Cl_2 (10 mL) was then added dropwise. After the mixture had been stirred for 45 min at -78°C , the reaction was completed by addition of triethylamine (12.8 mL, 92.1 mmol) and by allowing the reaction to warm to room temperature over a period of 30 min. The mixture was extracted with saturated aqueous NH_4Cl , washed with brine, dried with Na_2SO_4 and concentrated in vacuo to yield **29** (2.67 g, 95%) as a colourless oil. $[\alpha]_{\text{D}}^{23} = +0.9$ (c = 1.00, MeOH). ^1H NMR (CDCl_3 , 300 MHz): δ = 9.73 (d, J = 0.9 Hz, 1 H), 5.72 (m, 1 H), 5.08 (d, J = 11.1 Hz, 1 H), 5.03 (dd, J = 17.1, J = 1.8 Hz, 1 H), 4.47 (dd, J = 5.6, 0.9 Hz, 1 H), 4.41/4.29 (2 s, 1 H), 2.43 (m, 1 H), 2.32 (m, 1 H), 1.70 (s, 3 H), 1.52 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 198.5, 151.5, 133.8, 118.7, 94.2, 80.6, 58.7, 35.1/34.9, 28.3, 27.2/26.6, 24.7/23.5 ppm. IR (film): $\tilde{\nu}$ = 3406 (br. s), 1697 (s), 1674 (s) cm^{-1} . LRMS (FAB, m/z): 270. HRMS (FAB, m/z): calcd. $\text{C}_{14}\text{H}_{24}\text{O}_4\text{N}$ [$\text{M} + \text{H}^+$] 270.1705, found 270.1699.

(all*S*)-tert-Butyl 4-Allyl-5-(1'-hydroxy-1'-thiazol-2''-ylmethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (30): A solution of **29** (2.60 g, 9.65 mmol) in CH_2Cl_2 (70 mL) was cooled to 0°C , and 2-(trimethylsilyl)thiazole (1.54 mL, 9.65 mmol) was added. The reaction mixture was stirred for 12 h at 23°C and the solvent was evaporated. In order to deprotect partially silylated product **31**, the residue was dissolved in THF (10 mL), tetrabutylammonium fluoride (1.0 M, 9.65 mL, 9.65 mmol) was added, and the mixture was stirred for 20 min at room temperature. Evaporation of solvent and chromatographic purification (silica, 30% EtOAc in hexanes) of the residue afforded **30** (2.90 g, 85%) as a colourless oil. $[\alpha]_{\text{D}}^{23} = +8.6$ (c = 1.17, MeOH). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.74 (d, J = 3.0 Hz, 1 H), 7.35 (d, J = 3.0 Hz, 1 H), 5.93 (m, 1 H), 5.13–5.01 (m, 3 H), 4.40–4.10 (m, 3 H), 2.65 (m, 1 H), 2.43 (m, 1 H), 1.61/1.57 (2 s, 3 H), 1.50/1.45 (2 s, 3 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 170.4, 152.0/151.7, 141.2, 135.8/135.6, 120.2, 116.8/116.4, 94.1/93.5, 79.9/79.7, 78.5, 69.0, 58.1, 34.8/34.5, 28.3, 27.6/26.9, 24.9/23.6 ppm. IR (film): $\tilde{\nu}$ = 3387 (br. s), 1695 (s)

cm^{-1} . LRMS (FAB, m/z): 355. HRMS (FAB, m/z): calcd. $\text{C}_{17}\text{H}_{27}\text{O}_4\text{N}_2\text{S}$ [$\text{M} + \text{H}^+$] 355.1692, found 355.1702.

(all*S*)-tert-Butyl 4-Allyl-5-(1'-benzyloxy-1'-thiazol-2''-ylmethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (32): Sodium hydride (213 mg, 5.33 mmol) was added portionwise to a solution of **30** (1.57 g, 4.44 mmol), benzyl bromide (528 μL , 4.44 mmol) and tetrabutylammonium iodide (1.80 g, 4.88 mmol) in THF (100 mL), and the resulting mixture was heated under reflux for 1 h. After removal of solvent, subsequent addition of brine and extraction with CH_2Cl_2 , the organic layer was dried with Na_2SO_4 and concentrated in vacuo. Chromatographic purification (silica, 20% EtOAc in hexanes) gave **32** (1.87 g, 95%) as a colourless oil. $[\alpha]_{\text{D}}^{23} = -15.2$ (c = 4.07, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.82 (d, J = 3.0 Hz, 1 H), 7.44 (d, J = 3.0 Hz, 1 H), 7.44–7.26 (m, 5 H), 5.86 (m, 1 H), 5.07–4.90 (m, 3 H), 4.42 (s, 2 H), 4.37 (m, 1 H), 4.18 (dd, J = 10.8, 5.7 Hz, 1 H), 2.50–2.29 (m, 2 H), 1.54/1.50 (2 s, 3 H), 1.44 (s, 9 H), 1.43/1.40 (2 s, 3 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 170.1, 152.0/151.6, 142.3, 137.1/136.9, 135.5, 128.4, 128.1/128.0, 127.8/127.6, 120.4, 116.4/116.0, 93.6/93.1, 79.9/79.6, 79.0/78.7, 76.1, 70.6/70.5, 58.0, 34.7/34.3, 28.3, 27.5/26.7, 24.6/23.2 ppm. IR (film): $\tilde{\nu}$ = 1696 (s) cm^{-1} . LRMS (FAB, m/z): 445. HRMS (FAB, m/z): calcd. $\text{C}_{24}\text{H}_{33}\text{O}_4\text{N}_2\text{S}$ [$\text{M} + \text{H}^+$] 445.2161, found 445.2184.

(all*S*)-tert-Butyl [1-(2-Benzyloxy-1'-hydroxy-2'-thiazol-2''-ylethyl)-but-3-enyl]carbamate (33): A solution of **32** (27.0 mg, 60.7 μmol) and *p*-TsOH $\cdot\text{H}_2\text{O}$ (2.3 mg, 12.1 μmol) in MeOH (3 mL) was stirred for 24 h at ambient temperature. Extraction with saturated aqueous NaHCO_3 and CH_2Cl_2 , drying of the organic layer with Na_2SO_4 and concentration in vacuo gave **33** (22.5 mg, 95%) as a colourless film. $[\alpha]_{\text{D}}^{23} = -90.0$ (c = 0.50, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 7.80 (d, J = 3.2 Hz, 1 H), 7.41 (d, J = 3.2 Hz, 1 H), 7.38–7.30 (m, 5 H), 5.75 (m, 1 H), 5.03 (m, 2 H), 4.77 (br. m, 1 H), 4.75 (d, J = 7.1 Hz, 1 H), 4.58 (ABq, 2 H, J = 11.5 Hz, $\Delta\nu$ = 111.1 Hz), 4.03 (br. m, 1 H), 3.92 (br. s, 1 H), 2.28 (m, 1 H), 2.22 (m, 1 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 171.6, 156.4, 142.8, 137.2, 135.3, 129.0, 128.8, 128.6, 120.6, 117.9, 79.9, 78.7, 76.3, 72.4, 52.3, 34.3, 28.7 ppm. IR (film): $\tilde{\nu}$ = 3400 (br. s), 1707 (s) cm^{-1} .

(all*S*)-tert-Butyl 4-Allyl-5-(1'-benzyloxy-1'-carboxymethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (3): Molecular sieves (4 Å, 5.00 g) and methyl trifluoromethanesulfonate (0.55 mL, 4.83 mmol) were added to a solution of **32** (1.65 g, 3.71 mmol) in MeCN (80 mL) and the resulting mixture was stirred at 23°C for 30 min. The solvent was evaporated, the obtained residue was taken up into MeOH (150 mL), the mixture was cooled to 0°C , sodium borohydride (210 mg, 5.57 mmol) was added, and the reaction mixture was stirred for 30 min at 23°C . Acetone (100 mL) was added in order to quench excess hydride. The mixture was filtered through a short path of Celite[®], which was subsequently rinsed with MeOH, and the filtrate was concentrated in vacuo. The residue was dissolved in MeCN (60 mL) and water (6 mL), followed by addition of copper(II) oxide (2.95 g, 37.1 mmol). With vigorous stirring, copper(II) chloride dihydrate (0.63 g, 3.71 mmol) was added portionwise over a period of 5 min. After a further 5 min, the mixture was filtered through Celite[®] and the filter cake was washed several times with CH_2Cl_2 . The filtrate was dried with Na_2SO_4 and concentrated in vacuo to afford (all*S*)-tert-butyl 4-allyl-5-(1'-benzyloxy-2'-oxoethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1.12 g, 82%) as a colourless oil. $[\alpha]_{\text{D}}^{23} = -4.26$ (c = 3.40, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 9.73 (d, J = 7.5 Hz, 1 H), 7.37 (m, 5 H), 5.82 (m, 1 H), 5.04 (m, 2 H), 4.57 (ABq, 2 H, J = 11.7 Hz, $\Delta\nu$ = 54.0 Hz), 4.25–3.72 (m, 3 H), 2.43–2.28 (m, 2 H), 1.70/1.61 (2 s,

3 H), 1.57/1.52 (2 s, 3 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 200.9, 152.1/152.0, 137.1, 135.6, 129.0, 128.8, 128.4, 117.2/116.9, 94.5/93.9, 80.6, 80.5/80.3, 75.4/75.2, 72.8/72.6, 58.2, 35.2/34.8, 28.8, 28.0/27.3, 25.4/24.1 ppm. IR (film): $\tilde{\nu}$ = 1739 (s), 1696 (s) cm^{-1} . LRMS (FAB, m/z): 390. HRMS (FAB, m/z): calcd. $\text{C}_{22}\text{H}_{32}\text{O}_5\text{N}$ [$\text{M} + \text{H}^+$] 390.2281, found 390.2287. A mixture of (all*S*)-*tert*-butyl 4-allyl-5-(1'-benzyloxy-2'-oxoethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (0.42 g, 1.08 mmol), 2-methyl-2-butene (4 mL), sodium chlorite (1.27 g, 14.0 mmol) and $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (1.93 g, 14.0 mmol) in *t*BuOH (25 mL) and water (5 mL) was stirred for 2 h at room temperature. Saturated aqueous NH_4Cl was added, *t*BuOH was evaporated, and the aqueous layer was extracted with CH_2Cl_2 . The extract was dried with Na_2SO_4 and concentrated in vacuo to afford **3** (0.43 g, 98%) as a highly viscous oil. $[\alpha]_D^{23}$ = -13.2 (c = 2.50, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 7.35 (m, 5 H), 5.82 (m, 1 H), 5.01 (m, 2 H), 4.66 (d, J = 11.0 Hz, 1 H), 4.46 (d, J = 11.0 Hz, 1 H), 4.31 (m, 1.5 H), 4.12 (m, 1.5 H), 2.40–2.28 (m, 2 H), 1.60/1.57 (2 s, 3 H), 1.52/1.49 (2 s, 3 H), 1.48/1.45 (2 s, 9 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 174.9, 152.5/152.1, 136.9/136.8, 135.7, 128.9, 128.8, 128.5, 117.1/116.7, 94.4/93.9, 80.8/80.4, 76.5, 76.2/76.0, 72.8/72.6, 58.1, 35.1/34.7, 28.8, 28.0/27.3, 25.3/24.0 ppm. IR (film): $\tilde{\nu}$ = 1742 (m), 1670 (s) cm^{-1} . LRMS (FAB, m/z): 406. HRMS (FAB, m/z): calcd. $\text{C}_{22}\text{H}_{32}\text{O}_6\text{N}$ [$\text{M} + \text{H}^+$] 406.2230, found 406.2244.

(all*S*)-*tert*-Butyl 4-Allyl-5-{benzyloxy[1'-(8''-methoxy-1''-oxoisochroman-3''-yl)-3'-methylbutylcarbamoyl]methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (34): Trifluoroacetic acid (10 mL) was added at 0 °C to a solution of **2** in CH_2Cl_2 (40 mL). The reaction mixture was stirred for 10 min at 0 °C and concentrated to complete dryness in vacuo. A solution of **3** (402 mg, 1.00 mmol), EDCI (190 mg, 1.00 mmol) and DMAP (484 mg, 3.96 mmol) in CH_2Cl_2 (25 mL) was added, and the mixture was stirred for 6 h at room temperature. The reaction mixture was extracted with saturated aqueous NH_4Cl , dried with Na_2SO_4 , concentrated in vacuo and chromatographically purified (silica, 40% EtOAc in hexanes) to give **34** (460 mg, 72%) as a white solid. M.p. 72 °C. $[\alpha]_D^{23}$ = -95.4 (c = 2.55, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 7.48 (dd, J = 8.5, 7.5 Hz, 1 H), 7.37–7.27 (m, 4 H), 7.23 (m, 1 H), 6.93 (d, J = 8.5 Hz, 1 H), 6.78 (d, J = 7.5 Hz, 1 H), 6.48 (m, 1 H), 5.81 (m, 1 H), 5.00 (m, 2 H), 4.63 (m, 1 H), 4.48 (m, 1 H), 4.43 (m, 2 H), 4.25 (m, 1.5 H), 4.06 (m, 0.5 H), 4.02 (d, J = 7.9 Hz, 1 H), 3.98 (s, 3 H), 3.04 (dd, J = 15.2, 13.4 Hz, 1 H), 2.72 (dd, J = 15.1, 5.8 Hz, 1 H), 2.39–2.24 (m, 2 H), 1.90 (m, 1 H), 1.66 (m, 1 H), 1.48–1.31 (m, 16 H), 0.97 (m, 6 H) ppm. ^{13}C NMR (CHCl_3 , 75 MHz): δ = 169.9, 162.2, 161.0, 151.8/151.5, 142.0, 136.4/136.3, 135.4, 134.8, 128.7, 128.5, 128.3, 119.2, 116.5/116.1, 113.1, 110.7, 93.5/93.1, 79.9/79.7, 79.6, 76.6, 76.4/76.1, 72.3/72.1, 57.7/57.6, 56.1, 48.7, 40.5, 34.9/34.5, 31.6, 28.3, 27.5/26.8, 24.7, 24.6/23.3, 23.1, 21.7 ppm. IR (film): $\tilde{\nu}$ = 3313 (br), 1723 (s), 1691 (s) cm^{-1} . LRMS (FAB, m/z): 651. HRMS (FAB, m/z): calcd. $\text{C}_{37}\text{H}_{51}\text{O}_8\text{N}_2$ [$\text{M} + \text{H}^+$] 651.3645, found 651.3695.

(all*S*)-*tert*-Butyl 4-Benzoyloxycarbonylmethyl-5-{benzyloxy[1'-(8''-methoxy-1''-oxoisochroman-3''-yl)-3'-methylbutylcarbamoyl]methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (35): A solution of **34** (300 mg, 0.46 mmol) in CH_2Cl_2 (50 mL) was cooled to -78 °C. Ozone was passed through the solution until the blue colour persisted. Oxygen and nitrogen were successively passed through the solution for at least 10 min each. PPh_3 (121 mg, 0.46 mmol) was added portionwise under N_2 and the reaction mixture was allowed to warm to room temperature over a period of 1 h. Evaporation of solvent and chromatographic purification (silica, 50% EtOAc in hexanes) of the residue yielded (all*S*)-*tert*-butyl 5-

{benzyloxy[1'-(8''-methoxy-1''-oxoisochroman-3''-yl)-3'-methylbutylcarbamoyl]methyl}-2,2-dimethyl-4-(2'-oxoethyl)-1,3-oxazolidine-3-carboxylate (294 mg, 98%) as a colourless oil. $[\alpha]_D^{23}$ = -105.8 (c = 0.68, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 9.60 (d, J = 2.7 Hz, 1 H), 7.48 (dd, J = 8.4, 7.6 Hz, 1 H), 7.37–7.22 (m, 5 H), 6.94 (d, J = 8.5 Hz, 1 H), 6.78 (d, J = 7.5 Hz, 1 H), 6.52 (m, 1 H), 4.68–4.08 (m, 6 H), 4.00 (m, 1 H), 3.98 (s, 3 H), 3.06–2.51 (m, 3 H), 1.89 (m, 2 H), 1.68 (m, 1 H), 1.48–1.30 (m, 16 H), 0.97 (d, J = 8.3 Hz, 6 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 200.1, 170.0/169.8, 162.5, 161.6, 151.7/150.7, 142.4, 136.5, 135.2, 129.5, 129.2, 129.0, 119.7, 113.7, 111.2, 94.4/94.0, 81.3/80.9, 80.0, 76.9, 76.6/76.1, 73.3/72.8, 56.7, 55.2, 49.2, 45.1, 41.0, 32.1, 28.7, 27.3/25.3, 25.1, 25.0/23.8, 23.5, 22.2 ppm. IR (film): $\tilde{\nu}$ = 3311 (br), 1725 (s), 1690 (s) cm^{-1} . LRMS (FAB, m/z): 653. HRMS (FAB, m/z): calcd. $\text{C}_{36}\text{H}_{49}\text{O}_9\text{N}_2$ [$\text{M} + \text{H}^+$] 653.3438, found 653.3458. A mixture of (all*S*)-*tert*-butyl 5-{benzyloxy-[1'-(8''-methoxy-1''-oxoisochroman-3''-yl)-3'-methylbutylcarbamoyl]methyl}-2,2-dimethyl-4-(2'-oxoethyl)-1,3-oxazolidine-3-carboxylate (187 mg, 0.29 mmol), 2-methyl-2-butene (1 mL), sodium chlorite (335 mg, 3.70 mmol) and $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (511 mg, 3.70 mmol) in *t*BuOH (10 mL) and water (2 mL) was stirred for 1 h at room temperature. Saturated aqueous NH_4Cl was added, *t*BuOH was evaporated and the aqueous layer was extracted with CH_2Cl_2 . The extract was dried with Na_2SO_4 and concentrated in vacuo to afford (all*S*)-*tert*-butyl 5-{benzyloxy-[1'-(8''-methoxy-1''-oxoisochroman-3''-yl)-3'-methylbutylcarbamoyl]methyl}-4-carboxymethyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (189 mg, 99%) as a viscous oil. $[\alpha]_D^{23}$ = -97.5 (c = 0.41, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 7.47 (dd, J = 8.6, 7.5 Hz, 1 H), 7.32 (d, J = 7.4 Hz, 2 H), 7.23 (dd, J = 7.4, 7.2 Hz, 2 H), 7.15 (m, 1 H), 6.93 (d, J = 8.5 Hz, 1 H), 6.76 (d, J = 7.5 Hz, 1 H), 6.71 (m, 1 H), 4.55–4.29 (m, 5 H), 4.19 (d, J = 6.6 Hz, 1 H), 3.96 (s, 3 H), 3.65 (m, 1 H), 2.90 (m, 1 H), 2.69 (m, 2 H), 2.45 (m, 1 H), 1.87 (m, 1 H), 1.69 (m, 1 H), 1.48–1.26 (m, 16 H), 0.97 (d, J = 8.3 Hz, 6 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz, 315 K): δ = 174.3, 170.0, 162.7, 161.6, 151.7/150.7, 142.5, 136.9, 135.2, 128.9, 128.5, 119.7, 113.8, 111.3, 93.7, 80.9/80.7, 80.0, 76.8, 74.7/73.7, 72.3, 56.6, 56.3/56.2, 49.5, 41.0, 35.9, 32.1, 28.7, 26.8/26.7, 25.2, 23.4, 23.2/23.1, 22.3 ppm. IR (film): $\tilde{\nu}$ = 3318 (br. w), 1710 (br. s) cm^{-1} . LRMS (FAB, m/z): 691. HRMS (FAB, m/z): calcd. $\text{C}_{36}\text{H}_{48}\text{O}_{10}\text{N}_2\text{Na}$ [$\text{M} + \text{Na}^+$] 691.3207, found 691.3230. A solution of (all*S*)-*tert*-butyl 5-{benzyloxy[1'-(8''-methoxy-1''-oxoisochroman-3''-yl)-3'-methylbutylcarbamoyl]methyl}-4-carboxymethyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (190 mg, 0.28 mmol) and Cs_2CO_3 (46.0 mg, 0.142 mmol) in MeOH (10 mL) and water (2 mL) was stirred for 30 min at room temperature. Both solvents were evaporated and the resulting residue was dissolved in DMF (20 mL). Benzyl bromide (38.0 μg , 0.28 mmol) was added, and the reaction mixture was stirred for 12 h at room temperature. EtOAc was added and the mixture was washed with brine. The organic layer was dried with Na_2SO_4 , concentrated in vacuo and chromatographically purified (silica, 50% EtOAc in hexanes) to yield **35** (193 mg, 90%) a white solid. M.p. 74 °C. $[\alpha]_D^{23}$ = -83.6 (c = 1.35, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ = 7.47 (dd, J = 8.5, 7.5 Hz, 1 H), 7.34–7.17 (m, 10 H), 6.94 (d, J = 8.5 Hz, 1 H), 6.77 (d, J = 7.5 Hz, 1 H), 6.49 (m, 1 H), 5.05–4.30 (m, 8 H), 4.14 (m, 1 H), 3.98 (s, 3 H), 3.00–2.50 (m, 4 H), 1.86 (m, 1 H), 1.72 (m, 1 H), 1.52–1.35 (m, 16 H), 0.94 (m, 6 H) ppm. ^{13}C NMR (CHCl_3 , 125 MHz): δ = 171.3/170.9, 169.9, 162.6, 161.5, 152.1/151.5, 142.5, 136.9/136.8, 136.5/136.1, 135.2, 128.9–128.4, 119.7, 113.7, 111.2, 93.8/93.5, 80.9/80.6, 80.0/79.9, 76.8, 76.6/76.4, 73.1/72.6, 66.9/66.8, 56.7, 56.4/56.2, 49.3, 40.9, 36.2/35.7, 32.1, 28.8, 28.2/27.2, 25.1, 25.0/23.8, 23.4, 22.4/22.3 ppm. IR (film): $\tilde{\nu}$ = 3326 (br. w), 1733 (s), 1694 (s)

cm⁻¹. LRMS (FAB, *m/z*): 759. HRMS (FAB, *m/z*): calcd. C₄₃H₅₄O₁₀N₂Na [M + Na⁺] 781.3676, found 781.3702.

(allS)-tert-Butyl 4-Benzoyloxycarbonylmethyl-5-{benzyloxy[1'-(8''-hydroxy-1''-oxoisochroman-3''-yl)-3'-methylbutylcarbomoyl]-methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (36): A solution of **35** (106 mg, 0.14 mmol) and MgI₂ (74.0 mg, 0.27 mmol) in THF (5 mL) was heated to 40 °C for 30 min. The inorganic content was precipitated by addition of hexane, the mixture was filtered through a short path of silica, and the filter cake was rinsed with CH₂Cl₂. The filtrate was concentrated in vacuo to yield **36** (97.0 mg, 93%) as a colourless oil. [α]_D²³ = -43.0 (*c* = 0.65, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): δ = 10.90 (d, *J* = 6.6 Hz, 1 H), 7.44 (dd, *J* = 8.5, 7.5 Hz, 1 H), 7.40–7.14 (m, 10 H), 6.92 (d, *J* = 8.5 Hz, 1 H), 6.67 (d, *J* = 7.5 Hz, 1 H), 6.42 (m, 1 H), 5.03–4.80 (m, 2 H), 4.60–4.35 (m, 6 H), 4.19 (m, 1 H), 3.01–2.53 (m, 4 H), 1.71 (m, 1 H), 1.73 (m, 1 H), 1.47–1.34 (m, 16 H), 0.97 (m, 6 H) ppm. ¹³C NMR (CHCl₃, 125 MHz): δ = 171.4/171.0, 170.0/169.8, 162.6, 162.6, 152.1/151.4, 139.9, 137.0, 136.8, 136.4/136.0, 129.2–128.4, 118.5, 116.6, 108.4, 93.8/93.4, 81.8/81.7, 81.0/80.7, 76.9, 76.8/76.5, 73.3/72.8, 66.9/66.8, 56.3/56.1, 49.3, 41.1, 36.2/35.6, 30.6/30.1, 28.8, 28.0/27.0, 25.1, 25.0/23.8, 23.5, 22.3/22.2 ppm. IR (film): ν̄ = 3341 (br. w), 1734 (s), 1686 (s) cm⁻¹. HRMS (FAB, *m/z*): calcd. C₄₂H₅₂O₁₀N₂Na [M + Na⁺] 767.3520, found 767.3551.

AI-77-B (1): A mixture of **36** (32.0 mg, 43.0 μmol), Dowex® 50 W-X8-100 (2.00 g), palladium (10% on activated carbon, 4.0 mg), THF (5 mL) and MeOH (5 mL) was stirred for 10 h at 23 °C under hydrogen. Filtration through sand, evaporation of solvents and chromatographic purification (silica, MeOH) gave **1** (13.7 mg, 75%) as a white solid. M.p. 137–138 °C (ref.^[10] m.p. 139.5–140 °C). [α]_D²³ = -76.3 (*c* = 0.09, MeOH) {ref.^[16] [α]_D²² = -78.2 (*c* = 0.08, MeOH)}. ¹H NMR ([D₄]MeOH, 400 MHz): δ = 7.42 (dd, *J* = 8.4, 7.7 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 7.6 Hz, 1 H), 4.62 (ddd, *J* = 12.0, 3.2, 3.2 Hz, 1 H), 4.32 (ddd, *J* = 10.4, 3.2, 3.2 Hz, 1 H), 4.09 (d, *J* = 6.8 Hz, 1 H), 3.87 (dd, *J* = 6.8, 4.4 Hz, 1 H), 3.54 (ddd, *J* = 10.0, 4.4, 4.4 Hz, 1 H), 3.06 (dd, *J* = 16.4, 12.4 Hz, 1 H), 2.89 (dd, *J* = 16.4, 2.8 Hz, 1 H), 2.58 (dd, *J* = 17.2, 4.0 Hz, 1 H), 2.46 (dd, *J* = 16.8, 10.0 Hz, 1 H), 1.81 (ddd, *J* = 14.0, 12.0, 7.6 Hz, 1 H), 1.68 (m, 1 H), 1.40 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 1 H), 0.95 (d, *J* = 6.4 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H) ppm. ¹³C NMR ([D₄]MeOH, 125 MHz): δ = 177.2, 174.2, 170.0, 162.2, 140.5, 136.5, 118.5, 115.7, 108.4, 81.7, 72.2, 72.1, 51.6, 49.4, 39.7, 34.1, 29.8, 24.8, 22.8, 20.9 ppm. IR (film): ν̄ = 3301 (br. s), 1672 (s) cm⁻¹.

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