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New routes to β-cycloalkylalanine derivatives using serine-derived organozinc reagents

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Two distinct routes to β-cycloalkylalanine derivatives have been developed. The first route employs the reaction of the iodoalanine-derived zinc–copper reagent **2** with cycloalk-1-en-3-yl phosphates, and the second uses the palladium-catalysed coupling of the iodoalanine-derived zinc reagent **1** with cycloalkenyl triflates; in each case, catalytic hydrogenation of the unsaturated product leads to the protected β-cycloalkylalanine. The latter route allows access to a range of cycloalkyl derivatives, with ring sizes of 5–8. β-(1-Methyl-1-cyclohexyl)alanine may be prepared using reaction of the zinc–copper reagent **2** with 3-methyl-2-cyclohexenyl chloride, followed by hydrogenation. The corresponding cyclopentyl derivative may be prepared by reaction of the same zinc–copper reagent **2** with diethyl geranylphosphate, followed by ring-closing metathesis and hydrogenation.

Introduction

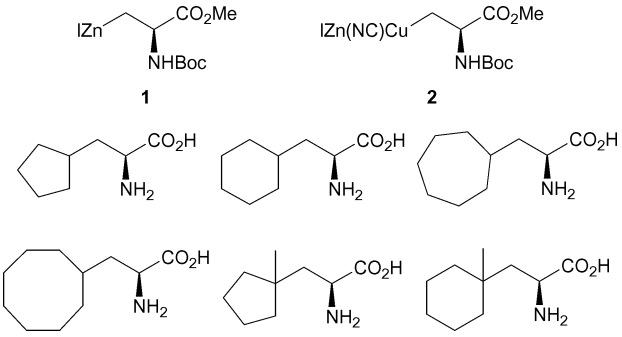
Non-natural analogues of proteinogenic amino acids are an important tool in the context of exploring receptor binding and preparing drug-like molecules able to interact with such receptors. Proteases, enzymes that cleave proteins or polyproteins at distinct sites, are involved in virtually all biological functions and dysfunctions. They regulate numerous biochemical, physiological and disease processes by controlling protein synthesis and degradation through hydrolysis of specific amide bonds in the polypeptide. A number of therapeutic areas have been addressed by the inhibition of proteases and physiological disorders. For example, a deficiency in cathepsin K can lead to pycnodysostosis, an autosomal recessive disorder while overexpression of cathepsin K may be responsible for excessive bone breakdown which is indicative for osteoporosis.[1]

Proteases recognise defined amino acid sequences adjacent to the cleavage site and the elucidation of this interaction is usually important in the design of either peptides or peptidomimetic molecules able to inhibit protease function.[2] Such inhibitors, containing natural and non-natural amino acids, can provide enhanced information on the best amino acids to fill the various enzyme pockets.

Whether employed in receptor exploration or peptide/peptidomimetic construction it is important that constituent amino acids, natural or non-natural, have a defined stereochemistry at the α carbon. Typically this will be the L-stereochemistry but a number of therapeutics also employ specific amino acids with D-stereochemistry at this position. Accordingly there is a need for efficient methodology allowing access to amino acids with defined stereochemistry at C-α. Although an enormous amount of effort has been devoted to developing such methods, substantial challenges still remain. Non-natural branched amino acids, especially compounds with highly lipophilic side chains, have recently started to attract attention as components of enzyme inhibitors.

While cyclohexylalanines, important as components of renin inhibitors,[3] may be prepared by catalytic reduction of the corresponding phenylalanine derivatives,[4] routes to cyclopentyl, cycloheptyl and cyclooctylalanines are less well-developed. A general route to these compounds using radical addition to dehydroalanine derivatives has been developed, yielding the products as racemates.[5] The synthesis of racemic cyclooctylalanine using glycine anion chemistry has also been reported.[6] A distinctive approach, involving the reaction of 9-alkylborabicyclononane derivatives with a glycine cation equivalent, followed by enantioselective protonation, has been applied to the preparation of cyclopentyl and cyclohexylalanines with moderate ee (62%).[7] The copper-catalysed ring-opening of a serinol-derived aziridine by cyclopentylmagnesium chloride, followed by oxidation, has also been reported.[8] The most general route presently available to enantiomerically pure cyclopentyl, cycloheptyl and cyclooctylalanines involves the electrophilic azidation of chiral imide enolates,[3,9] employing the method pioneered by Evans.[10]

We have previously reported a new route to lipophilic amino acids using the copper-catalysed reaction of the serine-derived organozinc reagent **1** with allylic halides, or by transmetallation of zinc reagent **1** to give the zinc–copper reagent **2**.[11] We now wish to report the application and extension of this approach to the preparation of protected derivatives of a range of non-natural branched amino acids containing a β-cycloalkyl residue, in which the stereochemistry is derived from serine.



1 **2**

Synthetic design

The most direct route to the targets above would require simple alkylation of either zinc reagent **1** or zinc–copper reagent **2** with the appropriate cycloalkyl halide. While recent significant developments in the area of palladium[12,13] and nickel[14–16] catalysed coupling of organozinc reagents with alkyl halides suggests that such an approach may be possible, we have initially explored two different routes which use the unsaturated isomeric compounds **3** and **4**, respectively, as intermediates (Scheme 1).

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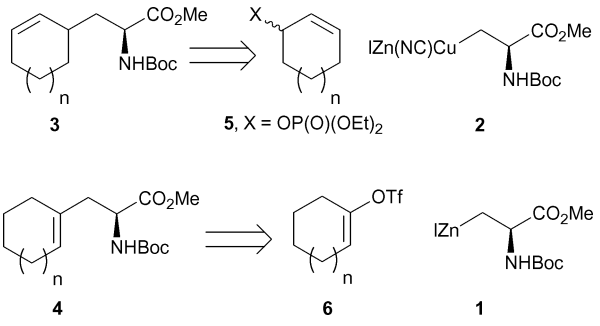
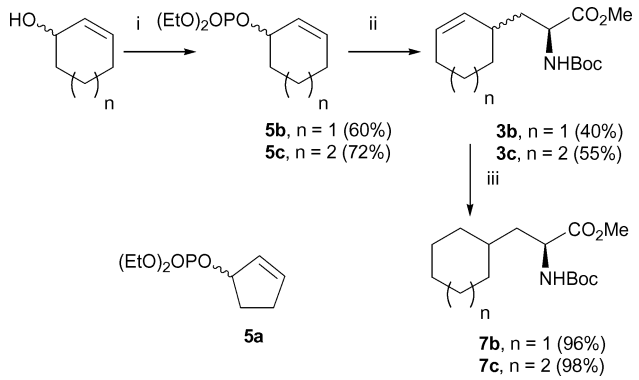


Scheme 1 Retrosynthetic plan.

Results and discussion

Allylation route

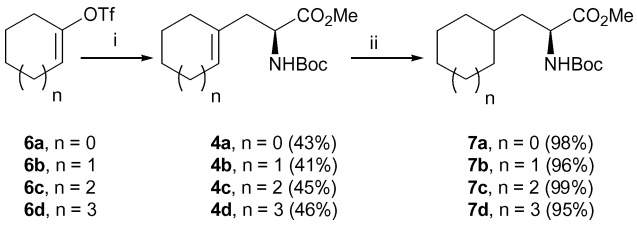
Given previous success using the allylation of the zinc–copper reagent **2**, initial efforts were directed towards the synthesis of the cycloalken-1-en-3-yl diethyl phosphates **5a–c**, X = $OP(O)(OEt)_2$. Phosphorylation, using pyridine and diethyl chlorophosphate, of the precursor alcohols, straightforwardly prepared by Luche reduction of the corresponding enones,[17] proved challenging. It has been reported that cyclohex-1-en-3-yl phosphate **5b** is not stable to silica gel chromatography,[18] but careful chromatographic purification using diethyl ether as eluent did allow **5b** to be isolated in pure form (60%). Preparation of **5c** was straightforward (72%), since it was perfectly stable to chromatographic purification, but all attempts to prepare the simple cyclopent-1-en-3-yl diethyl phosphate **5a** were unsuccessful.† While it would have been possible to explore the use of other less good leaving groups, the success of the vinylation route meant that this was not pursued. Treatment of the allylic phosphates **5b** and **5c** with the zinc–copper reagent **2**, prepared in DMF, resulted in the formation of the expected products **3b** and **3c** as a mixture of diastereoisomers, and in moderate yield. Careful control, especially of the reaction temperature, proved to be necessary. Catalytic hydrogenation of **3b** and **3c** gave the desired products **7b** and **7c**, respectively, in excellent yield (Scheme 2). While this route was effective for preparing the cyclohexyl and cycloheptyl analogues, the careful control of reaction conditions that was required meant that an alternative route was desirable.



Scheme 2 *Reagents and conditions*: i, $(EtO)_2POCl$, pyridine, CH_2Cl_2, 0 °C to rt, 16 h; ii, **2**, DMF, −30 °C to rt, 16 h; iii, H_2, Pd/C, MeOH.

Vinylation route

In earlier work, we had established that the palladium-catalysed coupling of an analogue of zinc reagent **1** with cyclohexenyl triflate **6b** did yield the expected cyclohexenylalanine, although the yield was modest (36%).[19] This general process has since been employed in the synthesis of neodysiherbaine A.[20] Given the recent improvements in yields that have been observed by preparing and coupling organozinc reagents in DMF as solvent,[21] further optimisation of this process seemed appropriate. In the event, palladium-catalysed coupling of zinc reagent **1** (prepared in DMF) with a series of cycloalkenyl triflates **6a–d** yielded the expected cycloalkenylalanine derivatives **4a–d** in modest, but consistent, yields. In all cases, the yields are based on the more valuable iodoalanine starting material from which the zinc reagent **1** was prepared, with the cycloalkenyl triflate being used in small excess (1.25 equiv.). When the coupling reaction between **1** and cycloheptenyl triflate was conducted on a larger scale (6 mmol) and at room temperature, the yield of product **4c** increased to 58%, again based on iodoalanine. Catalytic hydrogenation of **4a–d** gave the desired products **7a–d** respectively, in excellent yields (Scheme 3). This latter route ultimately proved to be a more effective and general route to the targets.



Scheme 3 *Reagents and conditions*: i, **1**, $Pd(PPh_3)_2Cl_2$ (5 mol%), DMF, 50 °C, 16 h; ii, H_2, Pd/C, MeOH.

Tertiary cycloalkyl analogues

In the context of our interest in more highly branched analogues of lipophilic amino acids,[11] synthesis of the additionally methylated cyclopentyl and cyclohexyl compounds **8a** and **8b** was considered. Self-evidently, only the allylation approach was possible, and the presumed enhanced instability of the required allylic phosphates **9a** and **9b**, compared to their non-methylated congeners **5a** and **5b** (Fig. 1), meant that an alternative was required.

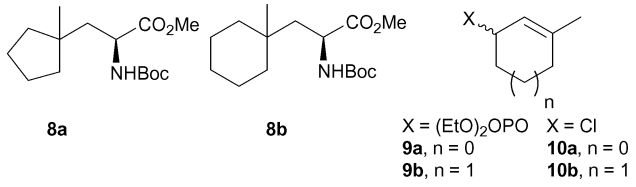
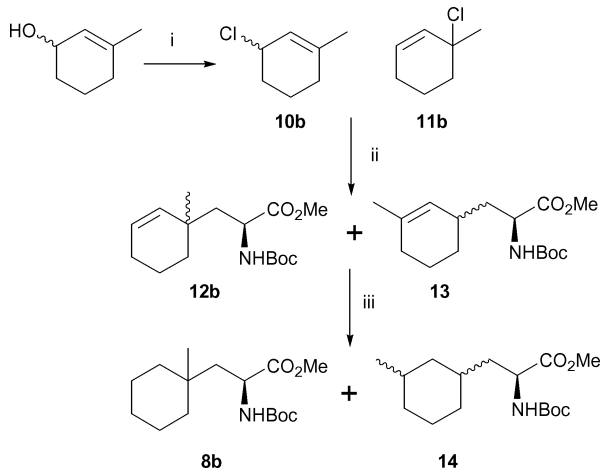


Fig. 1 (1-Methyl-1-cycloalkyl)alanine derivatives.

The first approach to be explored relied on the preparation of the cycloalkenyl chorides **10a** and **10b**. All efforts to prepare the cyclopentenyl derivative **10a** were frustrated, due to the great instability of the compound. However, it did prove possible to prepare the cyclohexenyl derivative **10b** by treatment of 3-methyl-2-cyclohexen-1-ol with thionyl chloride–pyridine in diethyl ether. The product was isolated as a 2.5 : 1 mixture with the product of allylic isomerisation, **11b**. Treatment of this mixture with the zinc–copper reagent **2** gave a mixture of allylation products **12b** (as a 1 : 1 mixture of diastereoisomers) and **13** (combined yield 53%), which was not separated but instead subjected to catalytic hydrogenation. The desired product **8b** could then be isolated (62%) straightforwardly. The remainder of the material was a mixture of diastereoisomers **14** resulting from hydrogenation of compound **13** (Scheme 4).

Since it was not possible to prepare the cyclopentenyl derivative **10a**, an entirely new route to **8a** was required. It appeared

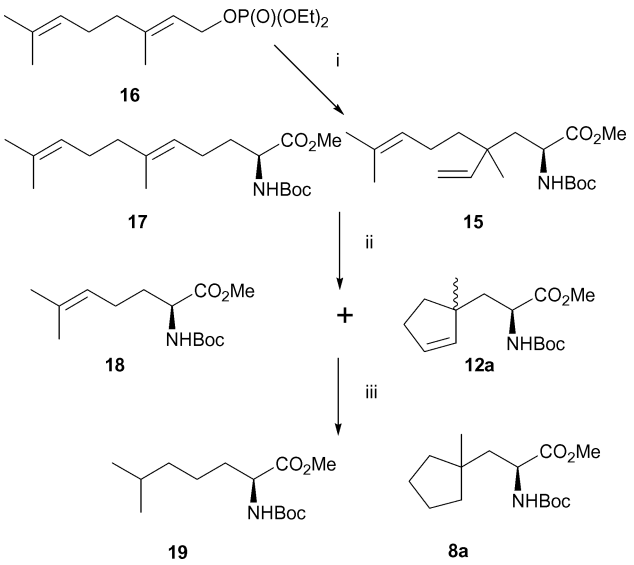
† This observation was somewhat unexpected, given the straightforward preparation of diethyl 2-iodo-2-cyclopentenyl-1-phosphate using the same method.[28]



Scheme 4 *Reagents and conditions*: i, $SOCl_2$, pyridine, Et_2O, 0 °C to rt, 16 h; ii, **2**, DMF, −30 °C to rt, 16 h; iii, H_2, Pd/C, MeOH.

that unsaturated intermediate **12a** could in principle be prepared by ring-closing metathesis (RCM)[22] of the allylation product **15**, itself available by reaction of diethyl geranylphosphate **16** with the zinc–copper reagent **2**.

In the event, treatment of zinc–copper reagent **2** with diethyl geranyl phosphate **16** yielded a mixture of three compounds, the formal product of S_N2 substitution **17** and the two diastereoisomeric S_N2' products **15**, with the latter predominating in a ratio of 88 : 12, and in a combined yield of 47%. These compounds could not be straightforwardly separated, but since this was not crucial to the planned route, the mixture was subjected to RCM using second-generation Grubbs' catalyst. This yielded a mixture of the cyclopentenyl adducts **12a** as a mixture of diastereoisomers, as well as a side product tentatively identified as the alkene **18**,[11] presumably derived by cross metathesis of **17** with the isopropylidene fragment formed as a side-product during the RCM of **15**. Hydrogenation of this mixture then gave the desired target **8a**, which was separated from compound **19** (derived by hydrogenation of **18**), and which was unambiguously identified by spectroscopic comparison with an authentic sample of **19** (Scheme 5).[11] The overall yield of **8a** for the RCM and hydrogenation steps from **15** was 84%. This route has been successfully scaled up to give 2 g of the product **8a**, demonstrating its practicality.



Scheme 5 *Reagents and conditions*: i, **2**, DMF, −30 °C to rt, 16 h; ii, 2nd generation Grubbs' catalyst (5 mol%), toluene, 80 °C, 16 h; iii, H_2, Pd/C, MeOH.

The success of this latter route suggests that a variety of 1-alkylcyclopentenes (and 1-alkylcyclopentanes) may also be prepared by the same strategy. The combination of (catalytic asymmetric) allylation of organometallic nucleophiles, followed by RCM, has been used before as a route to cyclopentene derivatives.[23]

In conclusion, a variety of routes to cycloalkyl alanine derivatives has been developed, further extending the breadth of application of serine-derived organometallic reagents.

Experimental

General experimental procedures have been previously described.[11] Dry DMF was distilled from calcium hydride and stored over 4 Å molecular sieves. Cycloalkenyl triflates were prepared by literature methods.[20,24] 3-Methyl-2-cyclohexen-1-ol was prepared by reduction of 3-methylcyclohex-2-enone using Luche conditions.[17]

General procedure for the synthesis of cycloalken-1-en-3-yl diethyl phosphates

Diethyl chlorophosphate (1.03 equiv.) was added to a solution of cycloalken-1-ol (1 equiv.) and pyridine (5.2 equiv.) in CH_2Cl_2 (5 cm^3) at 0 °C under a nitrogen atmosphere, and the mixture stirred for 1 h at 0 °C and then overnight at room temperature. The mixture was diluted with ether (50 cm^3) and washed with hydrochloric acid (3 × 10 cm^3, 1 M), brine (1 × 10 cm^3) and saturated sodium bicarbonate (1 × 10 cm^3) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product purified by flash chromatography using diethyl ether as solvent.

Cyclohexen-1-en-3-yl diethyl phosphate 5b[25]. Following the above procedure using 2-cyclohexen-1-ol (0.37 g, 3.76 mmol) the product **5b** was obtained as a colourless oil (0.52 g, 60% yield). δ_H (400 MHz, $CDCl_3$) 1.28 (6H, t, *J* 7.0, OCH_2CH_3), 1.53–1.60 (1H, m, CH_2), 1.71–1.75 (1H, m, CH_2), 1.80–2.06 (4H, m, CH_2), 4.03 (2H, q, *J* 7.0, OCH_2CH_3), 4.07 (2H, q, *J* 7.0, OCH_2CH_3), 4.82 [1H, br s, $CHOP(O)(OEt)_2$], 5.74 (1H, dd, *J* 10.0 and 1.5, CH), 5.88–5.92 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 16.0 (d, J_{CP} 7.0, OCH_2CH_3), 18.3 (CH_2), 24.6 (CH_2), 29.8 (d, J_{CP} 4.5, CH_2), 63.4 (d, J_{CP} 5.0, OCH_2CH_3), 72.1 [d, J_{CP} 5.5, $CHOP(O)(OEt)_2$], 126.2 (d, J_{CP} 5.0, CH), 132.6 (CH).

Cyclohepten-1-en-3-yl diethyl phosphate 5c. Following the above procedure using 2-cyclohepten-1-ol (0.46 g, 4.08 mmol) the product **5c** was obtained as a colourless oil (0.73 g, 72% yield). ν_{max} (liquid film)/cm^{-1} 2984, 2931, 1447, 1395, 1262, 1034, 1011, 981; δ_H (400 MHz, $CDCl_3$), 1.24 (3H, t, *J* 7.0, OCH_2CH_3), 1.25 (3H, t, *J* 7.0, OCH_2CH_3), 1.27–1.34 (1H, m, CH_2), 1.47–1.60 (2H, m, CH_2), 1.63–1.72 (1H, m, CH_2), 1.81–1.98 (3H, m, CH_2), 2.06–2.14 (1H, m, CH_2), 3.99 (2H, q, *J* 7.0, OCH_2CH_3), 4.01 (2H, q, *J* 7.0, OCH_2CH_3), 4.88–4.93 [1H, m, $CHOP(O)(OEt)_2$], 5.65–5.75 (2H, m, CH); δ_C (100 MHz, $CDCl_3$) 15.9 (d, J_{CP} 6.5, OCH_2CH_3), 26.1 (d, J_{CP} 4.5, CH_2), 28.3 (CH_2), 34.4 (d, J_{CP} 4.5, CH_2), 36.6 (CH_2), 63.5 (d, J_{CP} 5.5, OCH_2CH_3), 78.3 [d, J_{CP} 5.5, $CHOP(O)(OEt)_2$], 131.5 (CH), 133.9 (d, J_{CP} 5.0, CH).

General procedure for the synthesis of cycloalken-2-yl alanine amino acids 3

Zinc dust (0.294 g, 4.5 mmol) was placed in a 10 cm^3 round bottom flask equipped with a side arm, stirrer bar and fitted with a 3-way tap. The flask was evacuated and flushed with nitrogen 3 times. Dry DMF (0.5 cm^3) and TMSCl (0.1 cm^3) were added and the mixture was stirred for 35 min under a nitrogen atmosphere. The solvent was removed by syringe and the zinc dried under reduced pressure while heating with a heat gun. A solution of *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (0.247 g, 0.75 mmol) in dry DMF (0.3 cm^3) was prepared

under nitrogen, and this solution was transferred by syringe to the zinc, and the mixture stirred at 0 °C for 20 min. TLC (heptane : ethyl acetate, 1 : 1) confirmed that zinc insertion was complete.

In the meantime, a 10 cm^3 round bottomed flask equipped with a side arm and fitted with a 3-way tap was charged with CuCN (0.75 mmol) and dry lithium chloride (1.5 mmol) under nitrogen. Dry DMF (0.6 cm^3) was added and the resulting solution was cooled using a dry ice–acetonitrile bath (−30 °C). The solution of zinc reagent prepared previously was transferred carefully by syringe (avoiding the excess of zinc dust present) to the mixture of CuCN : LiCl (1 : 2) in DMF. The resulting mixture was warmed to 0 °C, and stirred for 5 min to allow the formation of the organocopper derivative **2**. Finally the electrophile **5** (1 mmol) was added and the mixture placed again in a dry ice–acetonitrile bath and stirred overnight (temperature increased slowly from −30 °C to room temperature). The reaction mixture was diluted with ethyl acetate and filtered through Celite®. The solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate (50 cm^3) and washed with saturated aqueous ammonium chloride solution (15 cm^3) and brine (15 cm^3). The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The two diastereoisomeric products **3** were obtained after purification by flash chromatography using a mixture of heptane and ethyl acetate (typically 3 : 1).

(2*S*,3*RS*)-2-*tert*-Butoxycarbonylamino-3-cyclohexen-2′-enylpropanoic acid methyl ester 3b. The product was obtained as an inseparable mixture of two diastereoisomers (A and A′, in 53 : 47 ratio) as a colourless oil (83 mg, 40%); *m*/*z* (EI) (Found MNa^+ 306.1686; $C_{15}H_{25}NO_4Na$ requires 306.1681) 322 (MK^+, 100%), MNa^+ 306 (6), 184 (16); ν_{max} (liquid film)/cm^{-1} 2929, 1747, 1715, 1517, 1437, 1366 and 1168; δ_H (400 MHz, $CDCl_3$) 1.18–1.30 (A and A′, 1H, m, CH_2), 1.41 [A, 9H, s, $C(CH_3)_3$], 1.42 [A′, 9H, s, $C(CH_3)_3$], 1.47–1.88 (A and A′, 5H, m, CH_2), 1.95–1.99 (A and A′, 2H, m, CH_2), 2.14–2.22 [A and A′, 1H, m, $CH(CH_2)_2CHCH$], 3.71 (A, 3H, s, OCH_3), 3.72 (A′, 3H, s, OCH_3), 4.34–4.42 (A and A′, 1H, m, $CHCO_2CH_3$) 4.90 (A, 1H, d, *J* 8.0, NH), 4.94 (A′, 1H, d, *J* 8.0, NH), 5.46 (A, 1H, dd, *J* 10.0 and 2.0, CH), 5.60 (A′, 1H, dd, *J* 10.0 and 2.0, CH), 5.67–5.73 (A and A′, 1H, m, CH); δ_C (100 MHz, $CDCl_3$) 20.9 (A, CH_2), 21.0 (A′, CH_2), 25.1 (A and A′, CH_2), 28.2 [A and A′, $C(CH_3)_3$], 29.1 (A and A′, CH_2), 31.4 [A, $CH(CH_2)_2CHCH$], 31.5 [A′, $CH(CH_2)_2CHCH$], 39.3 (A, CH_2CHNH), 39.4 (A′, CH_2CHNH), 51.4 (A, CO_2CH_3), 51.5 (A′, CO_2CH_3), 52.2 (A and A′, $CHCO_2CH_3$), 79.9 [A and A′, $C(CH_3)_3$], 128.0 (A and A′, CH), 129.9 (A, CH), 130.7 (A′, CH), 155.4 [A and A′, $NHCOC(CH_3)_3$], 173.8 (A and A′, CO_2CH_3).

(2*S*,3*RS*)-2-*tert*-Butoxycarbonylamino-3-cyclohepten-2′-enylpropanoic acid methyl ester 3c. The product was obtained as an inseparable mixture of two diastereoisomers (A and A′ in a 60 : 40 ratio) as a colourless oil (121 mg, 55%); *m*/*z* (EI) (Found MH^+ 298.2017 $C_{16}H_{28}NO_4$ requires 298.2018) MNa^+ 320 (11%), MH^+ 298 (6%), 242 (48), 198 (100); ν_{max} (liquid film)/cm^{-1} 2921, 1746, 1716, 1446, 1366 and 1164; δ_H (400 MHz, $CDCl_3$) 1.12–1.37 (A and A′, 2H, m, CH_2), 1.41 [A, 9H, s, $C(CH_3)_3$], 1.42 [A′, 9H, s, $C(CH_3)_3$], 1.49–1.67 (A and A′, 4H, m, CH_2), 1.75–1.92 (A and A′, 2H, m, CH_2), 2.06–2.12 (A and A′, 2H, m, CH_2), 2.28–2.38 [A and A′, 1H, m, $CH(CH_2)_2CHCH$], 3.71 (A and A′, 3H, s, OCH_3), 4.26–4.35 (A and A′, 1H, m, $CHCO_2CH_3$), 4.92 (A, 1H, d, *J* 8.5, NH), 4.96 (A′, 1H, d, *J* 8.5, NH), 5.47 (A, 1H, dd, *J* 10.5 and 3.5, CH), 5.55 (A′, 1H, dd, *J* 10.5 and 3.5, CH), 5.72–5.81 (A and A′, 1H, m, CH); δ_C (100 MHz, $CDCl_3$) 28.2 [A and A′, $C(CH_3)_3$], 28.4 (A, CH_2), 28.5 (A′, CH_2), 29.8 (A, CH_2), 29.9 (A′, CH_2), 32.1 (A and A′, CH_2), 33.5 (A and A′, CH_2), 35.7 [A, $CH(CH_2)_2CHCH$], 35.8 [A′, $CH(CH_2)_2CHCH$], 39.5 (A, CH_2CHNH), 39.6 (A′, CH_2CHNH), 51.7 (A and A′, $CHCO_2CH_3$), 52.0 (A, CO_2CH_3), 52.1 (A′, CO_2CH_3), 79.7 [A and A′, $C(CH_3)_3$], 132.0 (A, CH), 132.1 (A′, CH), 135.7 (A, CH), 136.5 (A′, CH), 155.3 [A and A′, $NHCOC(CH_3)_3$], 173.8 (A and A′, CO_2CH_3).

Synthesis of protected cycloalkyl alanine amino acids 7

A 0.1 M solution of the protected cycloalken-2-yl alanine amino acid **3** in methanol was treated with palladium (70 mg $mmol^{-1}$ of substrate, 10 wt% on activated carbon) and stirred vigorously under an atmosphere of hydrogen for 24 h. The catalyst was removed by filtration through Celite® and the solvent removed under reduced pressure to give the product **7**.

(2*S*)-2-*tert*-Butoxycarbonylamino-3-cyclohexylpropanoic acid methyl ester 7b. Following the above procedure using the mixture of the two diastereoisomers **3b** (43 mg, 0.15 mmol) the product **7b** was obtained as colourless oil (41 mg, 96%). $[\alpha]_D^{22}$ +2.0 (*c* 3.92 in $CHCl_3$); *m*/*z* (EI) (Found MNa^+ 308.1829; $C_{15}H_{27}NO_4Na$ requires 308.1838) MH^+ 308 (100%), 252 (3), 186 (19); ν_{max} (liquid film)/cm^{-1} 2924, 1715, 1516, 1366 and 1165; δ_H (400 MHz, $CDCl_3$) 0.83–0.98 (2H, m, CH_2), 1.10–1.30 (4H, m, CH_2), 1.43 [9H, s, $C(CH_3)_3$], 1.58–1.75 [6H, m, CH_2 + CH_AH_BCHNH + $CH(CH_2)_5$], 1.80 (1H, br d, *J* 13.5, CH_AH_BCHNH), 3.71 (3H, s, OCH_3), 4.27–4.36 (1H, m, $CHCO_2CH_3$), 4.86 (1H, d, *J* 8.0, NH); δ_C (100 MHz, $CDCl_3$) 26.1 (CH_2), 28.2 [$C(CH_3)_3$], 32.4 (CH_2), 33.7 [$CH(CH_2)_5$], 34.0 (CH_2), 40.3 (CH_2CHNH), 51.3 ($CHCO_2CH_3$), 52.1 (CO_2CH_3), 79.8 [$C(CH_3)_3$], 155.4 [$NHCOC(CH_3)_3$], 174.4 (CO_2CH_3).

(2*S*)-2-*tert*-Butoxycarbonylamino-3-cycloheptylpropanoic acid methyl ester 7c. Following the above procedure using the mixture of the two diastereoisomers **3c** (58 mg, 0.20 mmol) the product **7c** was obtained as colourless oil (57 mg, 98%). $[\alpha]_D^{22}$ +3.5 (*c* 6.0 in $CHCl_3$); *m*/*z* (EI) (Found MH^+ 300.2162; $C_{16}H_{30}NO_4$ requires 300.2175) MNa^+ 322 (4%), MH^+ 300 (61), 244 (100), 200 (11); ν_{max} (liquid film)/cm^{-1} 2926, 1717, 1507, 1367 and 1168; δ_H (400 MHz, $CDCl_3$) 1.15–1.22 (2H, m, CH_2), 1.44 (9H, s, $C(CH_3)_3$), 1.36–1.48 (3H, m), 1.52–1.70 (9H, m), 1.72–1.78 (1H, m, CH_AH_BCHNH), 3.72 (3H, s, OCH_3), 4.26–4.35 (1H, m, $CHCO_2CH_3$), 4.86 (1H, d, *J* 8.0, NH); δ_C (100 MHz, $CDCl_3$) 26.5 (CH_2), 28.2 [$C(CH_3)_3$], 33.7 ($CH(CH_2)_6$), 35.2 (CH_2), 35.7 (CH_2), 40.3 (CH_2CHNH), 52.1 ($CHCO_2CH_3$), 52.4 (CO_2CH_3), 80.0 ($C(CH_3)_3$), 155.6 ($NHCOC(CH_3)_3$), 174.5 (CO_2CH_3).

General procedure for the synthesis of protected cycloalken-1-yl alanine amino acids 4

Organozinc reagent **1** (1 equiv.) was prepared using the same procedure described in the preparation of **3**. The solution of organozinc reagent **1** was transferred carefully by syringe (avoiding the excess of zinc dust present) to a separate 25 cm^3 round bottom flask, equipped with a side arm, and which had been charged previously with dichlorobis(triphenylphosphine) palladium(II) (5 mol%), the cycloalken-1-yl triflate **6** (1.25 equiv.) and dry DMF (0.4 cm^3 per mmol of **1**) under a nitrogen atmosphere. Dry DMF (0.4 cm^3 per mmol of **1**) was added to the residual zinc dust and the washings were transferred to the reaction mixture. The mixture was stirred at 50 °C overnight, then cooled, diluted with ethyl acetate and filtered through Celite®. The solvent was removed under reduced pressure (primarily to remove traces of DMF which interfere with the aqueous work-up). The residue was diluted with ethyl acetate (200 cm^3) and washed with saturated aqueous ammonium chloride solution (50 cm^3), brine (50 cm^3). The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The product was obtained after purification by flash chromatography using heptane and ethyl acetate (typically 3 : 1) as eluent. In case of contamination of the product by triphenylphosphine, the crude product was dissolved in CH_2Cl_2 and washed with hydrogen peroxide, 10% aqueous sodium sulfite solution and water. The solution was dried over sodium sulfate and removed under reduced pressure.

(2*S*)-2-*tert*-Butoxycarbonylamino-3-cyclopent-1′-enyl-propanoic acid methyl ester 4a. Following the above procedure using *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (0.247 g, 0.75 mmol) the product **4a** was obtained by flash chromatography as a colourless oil (86 mg, 43% yield); $[\alpha]_D^{22}$ +13.9 (*c* 2.09 in $CHCl_3$); *m/z* (EI) (Found MNa^+ 292.1521; $C_{14}H_{23}NO_4Na$ requires 292.1525) MNa^+ 270 (13%), 214 (100), 169 (19), 153 (33); ν_{max} (liquid film)/cm^{-1} 1747, 1716, 1504 and 1336; δ_H (400 MHz, $CDCl_3$) 1.43 [9H, s, $C(CH_3)_3$], 1.84 (2H, qn, *J* 7.5, CH_2), 2.16–2.31 (4H, m, CH_2), 2.47 (1H, dd, *J* 14.0 and 8.0, CH_AH_BCHNH), 2.57 (1H, dd, *J* 14.5 and 5.5, CH_AH_BCHNH), 3.71 (3H, s, OCH_3), 4.35–4.42 (1H, m, $CHCO_2CH_3$), 4.95 (1H, d, *J* 7.5, NH), 5.43–5.47 (1H, br s, CH); δ_C (100 MHz, $CDCl_3$) 23.5 (CH_2), 28.3 [$C(CH_3)_3$], 32.4 (CH_2), 34.1 (CH_2), 34.7 (CH_2CHNH), 52.0 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 79.8 [$C(CH_3)_3$], 128.3 ($CHCH_2$), 138.9 [$CHC(CH_2)_2$], 155.2 [$NHCOC(CH)_3$], 173.1 (CO_2CH_3).

(2*S*)-2-*tert*-Butoxycarbonylamino-3-cyclohex-1′-enyl-propanoic acid methyl ester 4b. Following the above procedure using *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (0.123 g, 0.375 mmol) the product **4b** was obtained by flash chromatography as a colourless oil (43 mg, 41%); $[\alpha]_D^{22}$ +14.5 (*c* 1.68 in $CHCl_3$); *m/z* (EI) (Found MNa^+ 306.1668; $C_{15}H_{25}NO_4Na$ requires 306.1681) MNa^+ 306 (100%), 228 (26), 184 (25); ν_{max} (liquid film)/cm^{-1} 2930, 1747, 1716, 1505, 1366 and 1169; δ_H (400 MHz, $CDCl_3$) 1.42 [9H, s, $C(CH_3)_3$], 1.50–1.55 (2H, m, CH_2), 1.56–1.60 (2H, m, CH_2), 1.87–1.89 (1H, m, CH_2), 1.94–2.00 (3H, m, CH_2), 2.22 (1H, dd, *J* 13.5 and 8.5, CH_AH_BCHNH), 2.39 (1H, dd, *J* 13.5 and 5.5, CH_AH_BCHNH), 3.70 (3H, s, OCH_3), 4.31–4.39 (1H, m, $CHCO_2CH_3$), 4.88 (1H, d, *J* 7.0, NH), 5.42–5.48 (1H, br s, CH); δ_C (100 MHz, $CDCl_3$) 22.1 (CH_2), 22.7 (CH_2), 25.3 (CH_2), 27.8 (CH_2), 28.3 [$C(CH_3)_3$], 41.4 (CH_2CHNH), 51.9 ($CHCO_2CH_3$), 52.1 (CO_2CH_3), 79.8 [$C(CH_3)_3$], 125.7 ($CHCH_2$), 132.7 [$CHC(CH_2)_2$], 155.2 [$NHCOC(CH)_3$], 173.4 (CO_2CH_3).

(2*S*)-2-*tert*-Butoxycarbonylamino-3-cyclohept-1′-enyl-propanoic acid methyl ester 4c. Following the above procedure using *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (1.0 g, 3.04 mmol) the product **4c** was obtained by flash chromatography as a colourless oil (405 mg, 45%); $[\alpha]_D^{22}$ +7.8 (*c* 1.15 in $CHCl_3$); *m/z* (EI) (Found MH^+ 298.2013; $C_{16}H_{28}NO_4$ requires 298.2018) MK^+ 336 (100%), MH^+ 298 (71), 242 (91); ν_{max} (liquid film)/cm^{-1} 2923, 1747, 1717, 1499, 1418, 1367 and 1167; δ_H (400 MHz, $CDCl_3$) 1.36 [9H, s, $C(CH_3)_3$], 1.37–1.42 (4H, m, CH_2), 1.65 (2H, q, *J* 5.5, CH_2), 1.98–2.06 (4H, m, CH_2), 2.18 (1H, dd, *J* 14.0 and 8.5, CH_AH_BCHNH), 2.38 (1H, dd, *J* 14.0 and 5.5, CH_AH_BCHNH), 3.65 (3H, s, OCH_3), 4.21–4.29 (1H, m, $CHCO_2CH_3$), 4.84 (1H, d, *J* 7.0, NH), 5.54 (1H, t, *J* 6.0, CH); δ_C (100 MHz, $CDCl_3$) 26.3 (CH_2), 28.5 (CH_2), 28.6 [$C(CH_3)_3$], 33.6 (CH_2), 35.2 (CH_2), 35.6 (CH_2), 41.1 (CH_2CHNH), 52.1 ($CHCO_2CH_3$), 52.3 (CO_2CH_3), 80.1 [$C(CH_3)_3$], 118.3 ($CHCH_2$), 134.8 [$CHC(CH_2)_2$], 155.7 [$NHCOC(CH)_3$], 174.4 (CO_2CH_3).

Larger scale reaction

TMSCl (1.2 cm^3) was added to a stirred suspension of zinc dust (2.34 g, 36 mmol) in dry DMF (4 cm^3). The reaction mixture was stirred for 20 min, the zinc was allowed to settle and the supernatant then removed by syringe. The activated zinc was washed with dry DMF (2 × 1 cm^3), and then dried under reduced pressure to give a free flowing powder. *N*-(*tert*-Butoxycarbonyl)-3-iodo-L-alanine methyl ester (1.974 g, 6 mmol) was added as a solid to a rapidly stirred suspension of the activated zinc in dry DMF (4 cm^3) at room temperature under nitrogen. A strong exotherm was observed, and this was controlled with the aid of a water bath. Stirring was continued for 20 minutes, and the zinc was allowed to settle. The supernatant was then transferred by syringe into a flask containing cyclohepten-1-yl triflate (1.61 g, 6.6 mmol) and dichlorobis(triphenylphosphine)palladium(II) (210 mg, 0.3 mmol) under nitrogen. The zinc residue was washed with dry DMF (2 × 1 cm^3), and the washings also added to the reaction mixture. The reaction mixture was stirred for 16 hours at room temperature, and then transferred directly to a chromatography column, which was eluted with petroleum ether (bp 60–80 °C), 10% EtOAc, 15% EtOAc and finally 20% EtOAc in petroleum ether. The product **4c**, (R_f 0.4, 20% EtOAc in petroleum ether), was obtained as a colourless oil (1.027 g, 58%) (after separation of mixed fractions using the same solvent system). The major by-product was *N*-(*tert*-butoxycarbonyl)-L-alanine methyl ester (0.288 g, 24%, R_f 0.3), together with *N*-(*tert*-butoxycarbonyl)-dehydroalanine methyl ester (0.15 g, 12%, R_f 0.45).

(2*S*)-*tert*-Butoxycarbonylamino-3-cyclooct-1′-enyl-propanoic acid methyl ester 4d. Following the above procedure using *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (1 g, 3.04 mmol) the product **4d** was obtained as a colourless oil (435 mg, 46%); $[\alpha]_D^{22}$ +9.5 (*c* 0.53 in $CHCl_3$); *m/z* (EI) (Found MH^+ 312.2169; $C_{17}H_{30}NO_4$ requires 312.2175) MK^+ 350 (40%), MH^+ 312 (39), 256 (100), 212 (17); ν_{max} (liquid film)/cm^{-1} 2925, 1747, 1716, 1504, 1366 and 1171; δ_H (400 MHz, $CDCl_3$) 1.40 [9H, s, $C(CH_3)_3$], 1.41–1.45 (8H, m, CH_2), 2.05–2.12 (4H, m, CH_2), 2.24 (1H, dd, *J* 14.0 and 8.5 CH_AH_BCHNH), 2.48 (1H, dd, *J* 14.0 and 5.0, CH_AH_BCHNH), 3.71 (3H, s, OCH_3), 4.28–4.38 (1H, m, $CHCO_2CH_3$), 4.87 (1H, d, *J* 7.0, NH), 5.41 (1H, t, *J* 7.5, CH); δ_C (100 MHz, $CDCl_3$) 22.8 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 28.5 [$C(CH_3)_3$], 28.7 (CH_2), 29.8 (CH_2), 40.5 (CH_2CHNH), 52.1 ($CHCO_2CH_3$), 52.5 (CO_2CH_3), 80.0 [$C(CH_3)_3$], 128.8 ($CHCH_2$), 135.8 [$CHC(CH_2)_2$], 155.8 [$NHCOC(CH)_3$], 173.6 (CO_2CH_3).

General procedure for the synthesis of protected cycloalkyl alanine amino acids 7

A 0.1 M solution of the protected cycloalken-1-yl-alanine **4** in methanol was treated with palladium (70 mg $mmol^{-1}$ of substrate, 10 wt% on activated carbon) and stirred under an atmosphere of hydrogen for 24 h. The catalyst was removed by filtration through Celite® and the solvent removed under reduced pressure to give the product. If traces of water were observed, the product was redissolved in CH_2Cl_2 and dried over sodium sulfate.

(2*S*)-*tert*-2-Butoxycarbonylamino-3-cyclopentylpropanoic acid methyl ester 7a. Following the above procedure using the protected cyclopenten-1-yl alanine amino acid **4a** (42 mg, 0.16 mmol) the product **7a** was obtained as a colourless oil (41 mg, 98%); $[\alpha]_D^{22}$ +7.5 (*c* 0.81 in $CHCl_3$); *m/z* (EI) (Found MH^+ 272.1857; $C_{14}H_{26}NO_4$ requires 272.1862) MH^+ 272 (84%), 216 (100), 172 (40); ν_{max} (liquid film)/cm^{-1} 2923, 1747, 1716, 1504 and 1366; δ_H (400 MHz, $CDCl_3$) 1.03–1.16 (2H, m, CH_2), 1.44 [9H, s, $C(CH_3)_3$], 1.48–1.68 (6H, m, CH_2), 1.73–1.88 [3H, m, CH_2 + $CH(CH_2)_4$], 3.73 (3H, s, OCH_3), 4.25–4.32 (1H, m, $CHCO_2CH_3$), 4.93 (1H, d, *J* 7.0, NH); δ_C (100 MHz, $CDCl_3$) 25.0 (CH_2), 28.3 [$C(CH_3)_3$], 32.6 (CH_2), 36.6 [$CH(CH_2)_4$], 39.0 (CH_2CHNH), 52.1 ($CHCO_2CH_3$), 53.2 (CO_2CH_3), 79.8 [$C(CH_3)_3$], 155.3 [$NHCOC(CH)_3$], 173.8 (CO_2CH_3).

(2*S*)-*tert*-2-Butoxycarbonylamino-3-cyclohexylpropanoic acid methyl ester 7b. Following the above procedure using the protected cyclohexen-1-yl alanine amino acid **4b** (200 mg, 0.71 mmol) the product **7b** was obtained as a colourless oil (194 mg, 96%). The spectroscopic data of this compound matched that already obtained.

(2*S*)-*tert*-2-Butoxycarbonylamino-3-cycloheptylpropanoic acid methyl ester 7c. Following the above procedure using the protected cyclohepten-1-yl alanine amino acid **4c** (250 mg, 0.84 mmol) the product **7c** was obtained as a colourless oil

(248 mg, 99%). The spectroscopic data of this compound matched that already obtained.

(2*S*)-*tert*-2-Butoxycarbonylamino-3-cyclooctylpropanoic acid methyl ester 7d. Following the above procedure using the protected cycloocten-1-yl alanine amino acid **4d** (236 mg, 0.76 mmol) the product **7d** was obtained as a colourless oil (224 mg, 95%); $[\alpha]_D^{22}$ +6.5 (*c* 0.5 in $CHCl_3$); *m*/*z* (EI) (Found M^+ 314.2328; $C_{17}H_{32}NO_4$ requires 314.2331) MK^+ 352 (27%), MH^+ 314 (59), 258 (100), 214 (92); ν_{max} (liquid film)/cm^{-1} 2921, 1716, 1513, 1366 and 1172; δ_H (400 MHz, $CDCl_3$) 1.24–1.32 (2H, m, CH_2), 1.43 [9H, s, $C(CH_3)_3$], 1.42–1.49 (6H, m, CH_2), 1.56–1.68 [9H, m, CH_2 + $CH(CH_2)_7$], 3.72 (3H, s, OCH_3), 4.28–4.37 (1H, m, $CHCO_2CH_3$), 4.86 (1H, d, *J* 8.0, NH); δ_C (100 MHz, $CDCl_3$) 25.3 (CH_2), 26.5 (CH_2), 27.4 (CH_2), 28.5 [$C(CH_3)_3$], 31.2 (CH_2), 33.5 ($CH(CH_2)_7$), 41.2 (CH_2CHNH), 52.0 ($CHCO_2CH_3$), 52.3 (CO_2CH_3), 80.0 [$C(CH_3)_3$], 155.5 [$NHCOC(CH)_3$], 174.3 (CO_2CH_3).

3-Chloro-1-methyl-cyclohexene 10b[26]. A solution of 3-methylcycloalk-2-enol (670 mg, 5.93 mmol) and dry pyridine (0.45 cm^3, 7.41 mmol) in dry diethyl ether (3 cm^3) was cooled in an ice-bath. A solution of thionyl chloride (0.54 cm^3, 7.41 mmol) in dry diethyl ether (2 cm^3) was added. The mixture was stirred for 5 min at 0 °C and then for 3 h at room temperature, filtered, washed three times with aqueous saturated sodium hydrogen carbonate and brine. Drying over anhydrous magnesium sulfate and concentration under reduced pressure, gave the product **10b** (408 mg, 53%) as a yellow oil, as a 2.5 : 1 mixture with 3-chloro-3-methylcyclohexene **11b**. This mixture was used in the subsequent step without any further purification. δ_H (400 MHz, $CDCl_3$) 1.70 (3H, d, *J* 1.0, CH_3), 1.84–2.06 (6H, m, CH_2), 4.63–4.68 (1H, m, CHCl), 5.55–5.59 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 18.4 (CH_2), 23.7 (CH_3), 29.7 (CH_2), 32.0 (CH_2), 57.0 (CHCl), 122.6 (CH), 139.8 (CH).

(2*S*,3*RS*)-2-*tert*-Butoxycarbonylamino-3-(1-methyl-cyclohex-2-enyl)-propanoic acid methyl ester 12b. Organocopper derivative **2** was prepared from *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (0.247 g, 0.75 mmol) using the same procedure described in the preparation of **3**. The mixture of 3-chloro-1-methylcyclohex-1-ene and 3-chloro-3-methylcyclohex-1-ene (130 mg, 1 mmol) was added and the flask placed again in a dry ice–acetonitrile bath and stirred overnight (temperature increased slowly from −30 °C to room temperature). The reaction mixture was diluted with diethyl ether (50 cm^3) and filtered through Celite®. The solution was then washed with saturated aqueous ammonium chloride (15 cm^3) and brine (15 cm^3). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The product was obtained as a mixture of isomers (118 mg, 53%) after purification of the residue by flash chromatography using CH_2Cl_2 and ethyl acetate (10 : 1) as eluent. 2-*tert*-Butoxycarbonylamino-3-(1-methyl-cyclohex-2-enyl)-propanoic acid methyl ester **12b** (S_N2' products) and 2-*tert*-butoxycarbonylamino-3-(3-methyl-cyclohex-2-enyl)-propanoic acid methyl ester **13** (S_N2 product) were obtained in a ratio of 2.5 : 1. Subsequent purification of the mixture by flash chromatography using a mixture of CH_2Cl_2 : ethyl acetate (4 : 1) did allow the desired products **12b** to be isolated as a mixture of two diastereoisomers A and A′ in a 53 : 47 ratio: *m*/*z* (EI) (Found MH^+ 298.2018; $C_{16}H_{28}NO_4$ requires 298.2026) MH^+ 298 (28%), 242 (50), 198 (100); ν_{max} (liquid film)/cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.02 (A, 3H, s, CH_3), 1.03 (A′, 3H, s, CH_3), 1.42 [A, 9H, s, $C(CH_3)_3$], 1.43 [A′, 9H, s, $C(CH_3)_3$], 1.46–1.66 (A and A′, 4H, m, CH_2), 1.72–1.84 (A and A′, 2H, m, CH_2), 1.90–1.96 (A and A′, 2H, m, CH_2CHNH), 3.70 (A, 3H, s, OCH_3), 3.71 (A′, 3H, s, OCH_3), 4.32–4.41 (A and A′, 1H, m, $CHCO_2CH_3$), 4.81–4.90 (A and A′, 1H, m, NH), 5.38–5.43 (A and A′, 1H, br d, *J* 9.0, CH), 5.62 (A and A′, 1H, dt, *J* 9.0 and 3.5, CH); δ_C (100 MHz, $CDCl_3$) 18.8 (A, CH_2), 18.9 (A′, CH_2), 24.8 (A, CH_2), 24.9 (A′, CH_2), 27.5 (A, CH_3), 27.8 (A′, CH_3), 28.3 [A and A′, $C(CH_3)_3$], 34.1 [A, $C(CH_2)_2CH_3$], 34.4 [A′, $C(CH_2)_2CH_3$], 34.9 (A and A′, CH_2), 44.8 (A, CH_2CHNH), 45.2 (A′, CH_2CHNH), 50.9 (A and A′, $CHCO_2CH_3$), 52.1 (A, CO_2CH_3), 52.2 (A′, CO_2CH_3), 79.7 [A, $C(CH_3)_3$], 79.9 [A′, $C(CH_3)_3$], 126.3 (A and A′, CH), 135.1 (A, CH), 135.2 (A′, CH), 155.0 [A and A′, $NHCOC(CH)_3$], 174.2 (A and A′, CO_2CH_3).

(2*S*)-2-*tert*-Butoxycarbonylamino-3-(1-methyl-cyclohexyl)-propanoic acid methyl ester 8b. A solution of the mixture of diastereoisomers **12b** (42 mg, 0.141 mmol) in methanol (1.4 cm^3) was treated with palladium (10 mg, 10 wt% on activated carbon) and stirred under an atmosphere of hydrogen for 24 h. The catalyst was removed by filtration through Celite® and the solvent removed under reduced pressure to yield the product **8b** as a colourless oil (27 mg, 62%). $[\alpha]_D^{22}$ +1.3 (*c* 1.92 in $CHCl_3$); *m*/*z* (ES) (Found MNa^+ 322.1998; $C_{16}H_{29}NO_4Na$ requires 322.1994) MNa^+ 322 (100%); ν_{max} (liquid film)/cm^{-1} 2927, 2861, 1747, 1714, 1514, 1366 and 1166; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, s, CH_3), 1.26–1.32 (4H, m, CH_2), 1.38–1.43 (6H, m, CH_2), 1.42 [9H, s, $C(CH_3)_3$] 1.60–1.65 (1H, br d, *J* 14.0, CH_AH_BCHNH), 1.72 (1H, dd, *J* 14.0 and 3.5, CH_AH_BCHNH), 3.71 (3H, s, OCH_3), 4.34 (1H, dt, *J* 3.5 and 9.0, $CHCO_2CH_3$), 4.82 (1H, d, *J* 9.0, NH); δ_C (100 MHz, $CDCl_3$) 21.9 (CH_2), 24.6 [$C(CH_2)_3$], 26.2 (CH_2), 28.3 [$C(CH_3)_3$], 33.0 (CH_2), 37.8 (CH_2), 44.9 (CH_2CHNH), 50.4 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 79.8 [$C(CH_3)_3$], 155.1 [$NHCOC(CH)_3$], 174.6 (CO_2CH_3).

Phosphoric acid (*E*)-3,7-dimethyl-octa-2,6-dienyl ester diethyl ester 16[27]. Diethyl chlorophosphate (1.3 cm^3, 7.78 mmol) was added dropwise to a solution of geraniol (1 g, 6.48 mmol) and pyridine (2.1 cm^3, 26 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 1 h at 0 °C and then overnight at room temperature. The reaction mixture was diluted with diethyl ether (50 cm^3) and washed with hydrochloric acid (3 × 10 cm^3, 1 M), brine (1 × 10 cm^3) and saturated sodium bicarbonate (1 × 10 cm^3) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product purified by column chromatography over silica gel using diethyl ether as solvent, yielding geraniol phosphate **16** as a colourless oil (1.47 g, 78%). ν_{max} (liquid film)/cm^{-1} 2980, 2912, 1276, 1101 and 1035; δ_H (400 MHz, $CDCl_3$) 1.26 (6H, dt, *J* 7.0 and 1.0, OCH_2CH_3), 1.52 (3H, d *J* 0.5, CH_3CCH_2), 1.60 (3H, d, *J* 1.0, CH_3CHCH_3), 1.63 (3H, d, *J* 1.0, CH_3CHCH_3), 1.95–2.08 (4H, m, CH_2), 4.00–4.07 (4H, m, OCH_2CH_3), 4.49 (2H, dt, *J* 7.5 and 0.5, $CHCH_2O$), 4.98–5.03 (1H, m, $CHCH_2O$), 5.30–5.36 [1H, m, $CHC(CH_3)_2$]; δ_C (100 MHz, $CDCl_3$) 15.9 (J_{CP} 6.5, OCH_2CH_3), 16.2 (CH_3CCH_2), 17.5 (CH_3CHCH_3), 25.5 (CH_2CHC), 26.0 (CH_3CHCH_3), 39.3 (CH_2CCH_3), 63.4 (J_{CP} 6.0, OCH_2CH_3), 63.9 (J_{CP} 5.5, $CHCH_2O$), 118.8 (J_{CP} 6.5, $CHCH_2O$), 123.4 [$CHC(CH_3)_2$], 131.7 (CH_3CHCH_3), 142.3 (CH_2CCH_3CH).

Coupling of phosphoric acid (2*E*)-3,7-dimethyl-octa-2,6-dienyl ester diethyl ester 16 to reagent 2

Organocopper derivative **2** was prepared from *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (0.247 g, 0.75 mmol) using the same procedure described in the preparation of **3**. Geraniol phosphate **16** (290 mg, 1 mmol) was added and the mixture placed again in a dry ice–acetonitrile bath and stirred overnight (temperature increased slowly from −30 °C to room temperature). The reaction mixture was diluted with ethyl acetate and filtered through Celite®. The solvent was removed under reduced pressure (in order to remove residual DMF it was necessary to heat at 55 °C under reduced pressure and to leave the crude material attached to a vacuum pump for 2 h). The residue was diluted with ethyl acetate (50 cm^3) and washed with saturated aqueous ammonium chloride solution (15 cm^3) and brine (15 cm^3). The organic phase was dried over sodium sulfate and concentrated under reduced pressure. A mixture of **17** and **15**

(50 : 50 mixture of diastereoisomers) was obtained as colourless oil (120 mg, 47%) (with a ratio of **17** to **15** of 12 : 88, as determined by ^{1}H NMR) after purification by flash chromatography using heptane–ethyl acetate (3 : 1). NMR data were obtained as follows.

(2S,5*E*)-2-*tert*-Butoxycarbonylamino-6,10-dimethyl-undeca-5,9-dienoic acid methyl ester 17. δ_H (400 MHz, $CDCl_3$) 1.44 [9H, s, $C(CH_3)_3$], 1.58 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.77–1.88 (2H, m), 1.95–1.99 (2H, m), 2.01–2.08 (4H, m), 3.73 (3H, s, OCH_3), 4.24–4.33 (1H, m, $CHCO_2CH_3$), 4.96–5.03 (1H, br s, NH), 5.05–5.12 (2H, m).

(2*S*,4*RS*)-2-*tert*-Butoxycarbonylamino-4,8-dimethyl-4-vinyl-non-7-enoic acid methyl ester 15. Mixture of diastereoisomers A and A′ obtained in 50 : 50 ratio. δ_H (400 MHz, $CDCl_3$) 1.04 (A and A′, 3H, s, CH_3CCH_2), 1.33 (A and A′, 2H, t, *J* 8.0, CH_3CCH_2), 1.41 [A, 9H, s, $C(CH_3)_3$], 1.42 [A′, 9H, s, $C(CH_3)_3$], 1.57 (A and A′, 3H, s, CH_3CCH_3), 1.66 (A and A′, 3H, s, CH_3CCH_3), 1.77–1.90 (A and A′, 4H, m, CH_2CHNH + CH_2CHC), 3.68 (A, 3H, s, OCH_3), 3.70 (A′, 3H, s, OCH_3), 4.30 (A and A′, 1H, m, $CHCO_2CH_3$), 4.82 (A and A′, 1H, d, *J* 8.0, NH), 4.92–5.02 (A and A′, 2H, m, CH_2CHC), 5.02–5.10 [A and A′, 1H, m, $CHC(CH_3)_2$], 5.66–5.76 (A and A′, 1H, m, CH_2CHC). δ_C (100 MHz, $CDCl_3$) 17.8 (A and A′, CH_2CHC), 22.1 (A, CH_3CCH_3), 22.2 (A′, CH_3CCH_3), 22.8 (A, CH_3CCH_2), 22.9 (A′ CH_3CCH_2), 25.9 (A and A′, CH_3CCH_3), 28.6 [A and A′, $C(CH_3)_3$], 39.5 (A, CH_3CCH_2), 39.7 (A′, CH_3CCH_2), 41.4 (A, CH_3CCH_2), 41.5 (A′, CH_3CCH_2), 43.8 (A, CH_2CHNH), 44.0 (A′, CH_2CHNH), 51.1 (A and A′, $CHCO_2CH_3$), 52.3 (A and A′, OCH_3), 79.8 [A and A′, $C(CH_3)_3$], 112.7 (A, CH_2CHC), 113.1 (A′, CH_2CHC), 124.7 [A and A′, $CHC(CH_3)_2$], 131.6 [A and A′, $CHC(CH_3)_2$], 145.8 (A, CH_2CHC), 145.9 (A′, CH_2CHC), 155.2 [A and A′, $NHCOC(CH_3)_3$], 174.3 (A and A′, CO_2CH_3).

Ring closing metathesis of 15

Grubbs′ 2nd generation catalyst (11 mg, 5 mol%) was placed in a round bottom flask equipped with a magnetic stirrer bar under nitrogen. A solution of the mixture of **15** and **17** (70 mg, 0.206 mmol) in dry toluene (2 cm^3) was added, and the reaction mixture was heated at 80 °C for 16 h. After cooling, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (gradient 2–10% EtOAc in petroleum ether) to give an inseparable mixture (54 mg) (86 : 14 ratio) of (2*S*)-2-*tert*-butoxycarbonylamino-3-(1′-methyl-cyclopent-2′-enyl)-propanoic acid methyl ester **12a** (50 : 50 mixture of diastereoisomers) and (2*S*)-2-*tert*-butoxycarbonylamino-6-methylhept-5-enoic acid methyl ester **18** (tentatively identified as a component of the mixture by comparison with literature data[11]), which was used directly in the next step.

(2*S*)-2-*tert*-Butoxycarbonylamino-3-(1-methyl-cyclopentyl)-propanoic acid methyl ester 8a

A solution of the mixture of **12a** and **18** (56 mg) in methanol (2 cm^3) was treated with palladium (10 mg, 10 wt% on activated carbon) and stirred under an atmosphere of hydrogen for 24 h. The catalyst was removed by filtration through Celite® and the solvent removed under reduced pressure to give a mixture which was purified by flash chromatography using petroleum ether (40–60) : diethyl ether to give (2*S*)-2-*tert*-butoxycarbonylamino-6-methylheptanoic acid methyl ester **19**[11] and (2*S*)-2-*tert*-butoxycarbonylamino-3-(1-methyl-cyclopentyl)-propanoic acid methyl ester **8a** (45 mg, 73% overall yield from the mixture of **15** and **17**, and 84% overall yield based on the amount of **15**) as a colourless oil. $[\alpha]_D^{22}$ −1.8 (*c* 0.56 in $CHCl_3$); *m/z* (EI) (Found MH^+ 286.2024; $C_{15}H_{28}NO_4$ requires 286.2018) MH^+ 286 (1.5%), 230 (47), 186 (100); ν_{max} (liquid film)/cm^{-1} 2955, 1715, 1513, 1366 and 1166; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, s, CH_3C), 1.42 [9H, s, $C(CH_3)_3$], 1.34–1.45 (4H, m, CH_2), 1.53 (1H, dd, *J* 14.0 and 8.5, CH_AH_BCHNH), 1.57–1.68 (4H, m), 1.85 (1H, dd, *J* 13.5 and 4.0, CH_AH_BCHNH), 3.72 (3H, s, OCH_3), 4.36 (1H, dt, *J* 4.0 and 8.5, $CHCO_2CH_3$), 4.83 (1H, d, *J* 8.5, NH); δ_C (100 MHz, $CDCl_3$) 23.6 (CH_2), 24.0 (CH_3C), 24.8 (CH_3C), 28.3 [$C(CH_3)_3$], 39.8 (CH_2), 44.9 (CH_2CHNH), 51.7 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 79.8 [$C(CH_3)_3$], 155.1 [$NHCOC(CH_3)_3$], 174.4 (CO_2CH_3).

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