Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 14 (2006) 8323–8331
Bioorganic & Medicinal Chemistry

Synthesis of amino acid derived seven-membered lactams by RCM and their evaluation against HIV protease

Shazia Zaman,[a] Pietro Campaner[b] and Andrew D. Abell[a,*]

[a]*Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch, New Zealand*
[b]*Department of Chemical Sciences, University of Trieste, via Giorgieri I, 1-34127 Trieste, Italy*

Received 21 July 2006; revised 27 August 2006; accepted 7 September 2006
Available online 28 September 2006

Abstract—A versatile synthesis of hydroxylated and epoxy 1-azepin 2-ones substituted at N1, C-3 and C-4 or C-7 has been developed. The sequence involves ring-closing metathesis of an amino acid derived diene amide, followed by either epoxidation or dihydroxylation, of the resulting alkene. Assay of the product epoxides (**10**, **18**, **25**) and diols (**9a**, **17**, **24**) against HIV protease reveals micromolar inhibition.

1. Introduction

Medium-sized lactams are important components of natural products that possess many and varied biological properties, including antitumour, antibiotic, antithelmintic[1,2] and insecticidal activity.[3] They also find wide use in organic synthesis,[4] and as a basis of peptidomimetic scaffolds that accurately define and stabilize the biologically active conformations of peptides and proteins (e.g., HIV protease inhibitor **1**,[5] see Fig. 1). As such, a good deal of effort has focussed over the years on developing general synthetic approaches to simple monocyclic lactams-based on ring closure, ring expansion, cycloaddition and fragmentation reactions.[1] Lactamisation has traditionally been the method of choice for cyclisation,[6] however, ring-closing metathesis (RCM)[7] now provides access to highly functionalized lactams under mild conditions and with a high degree of functional group tolerance.[4c,8]

Metathesis has found particular importance in the construction of peptidomimetic lactams[8] and in this paper we report methodology for the synthesis of seven-membered unsaturated peptidomimetic ring lactams [1,3,4,7-tetrahydro 2H-azepin-2-one (**2**)] with substituents at N-1, C-3 and C-4 or C-7. The newly formed double bond at C-5 and C-6 is further derivatised either by epoxidation, or by conversion into a diol, to give a new class of HIV protease inhibitor. The design of the target lactams was based on the structure of some well-known HIV protease inhibitors, cyclic ureas[9a,b] (e.g., **3**); related cyclic sulfonamides[9b,c] (**4**) and phosphonamides;[9d] and six-membered lactams[4] (e.g., **5**). The six-membered lactams, while being structurally

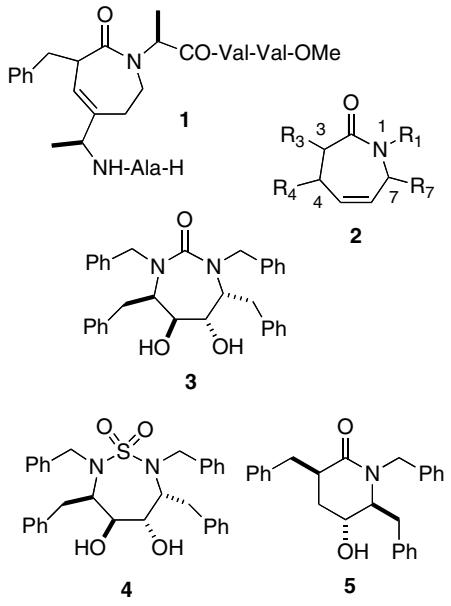


Figure 1.

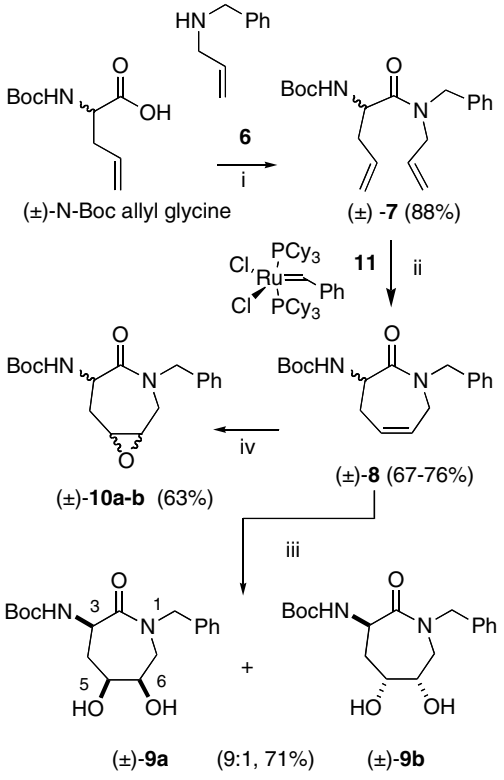
Keywords: Ring-closing metathesis; Lactams; Diol; HIV protease.
* Corresponding author. Tel.: +64 3 3642818; fax: +64 3 3632110; e-mail: andrew.abell@canterbury.ac.nz

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.09.009

well removed from the well-studied and potent cyclic ureas and sulfonamides, are difficult to prepare and are reported as weak inhibitors of HIV protease.[4a] By contrast seven-membered lactam-based HIV protease inhibitors, reported here for the first time, more closely resemble the cyclic ureas and sulfonamides provide a versatile framework for the further development of HIV protease inhibitors and other lactam-based peptidomimetics. The results of the assay of our compounds (**9a**, **10**, **17**, **18**, **24** and **25**) against HIV protease are presented, and discussed, as the first step to developing this class.

2. Results and discussion

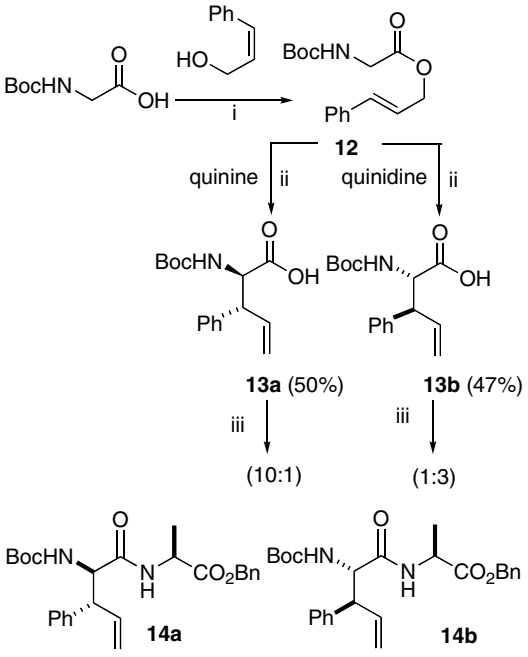
We initially targeted the simple racemic lactam **8** to demonstrate the feasibility of the RCM methodology (Scheme 1). The key precursor diene **7** was prepared as a mixture of rotamers in 88% yield by coupling (±)-*N*-Boc allyl glycine with allyl benzyl amine[10] **6** in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), hydroxybenzotriazole (HOBT) and *N*-methylpyrrolidone (NMP). This was then treated with Grubb's first-generation catalyst **11**,[11] in dry CH_2Cl_2, to give the cyclic lactam (±)-**8** in 76% yield. Introduction of a *cis*-diol into (±)-**8** was achieved by catalytic Sharpless *cis*-asymmetric dihydroxylation.[12] In particular, treatment of (±)-**8** with either $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL gave the same diastereomeric mixture of *cis* diols (±)-**9a** and (±)-**9b** (9:1, by integration of the *t*-Bu protons in the ^1H NMR spectrum) in 71% yield. The stereochemistry of the addition sequence would thus appear to be controlled by factors other than the nature of the ligand used. The most likely explanation is that facial selectivity is dictated by the relative configuration of the adjacent NH-Boc group, where addition is known to occur *syn* to such a group due to hydrogen bonding between the NH and the intermediate osmate ester.[13] The absolute configuration of the major product in which the diol and NH-Boc groups are *syn*, as defined by NOE data (see below) and drawn in **9a**, supports these assignments and conclusions.



Scheme 1. Reagents and conditions: (i) EDCI, HOBT, NMP, rt, 16 h; (ii) CH_2Cl_2, reflux, 24 h; (iii) $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, $K_2OsO_2(OH)_2$, K_2CO_3, $K_3(FeCN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C–rt, 48 h; (iv) Oxone®/acetone, H_2O, 0 °C–rt, 16 h.

The major diol (±)-**9a** was isolated as a white solid by fractional crystallization from the mixture and its relative configuration was determined on the basis of 2D NOE data. Positive enhancements were observed between H-3, H-5 and H-6 (see Scheme 1 for numbering) such that the substituents at these positions must be *syn*. The minor diastereoisomer (±)-**9b** could not be separated from (±)-**9a** by chromatography and was thus characterized as a mixture. The olefin (±)-**8** was also epoxidized on treatment with dimethyldioxirane (generated in situ from Oxone®/acetone)[14] to give the racemic epoxides **10** (63%) as a 1:1 mixture of diastereoisomers that could not be separated by chromatography (see Scheme 1 step iv).

With these results in hand we set about introducing a further aryl substituent at C-4 to better mimic known HIV protease inhibitors **3** and **4** (see later for a discussion). The key starting optically active acids (**13a** and **13b**) were prepared by Claisen rearrangement[15] of **12** (itself prepared in 92% by coupling (±)-*N*-Boc glycine to *Z*-cinnamoyl alcohol with DCC and DMAP in CH_2Cl_2)

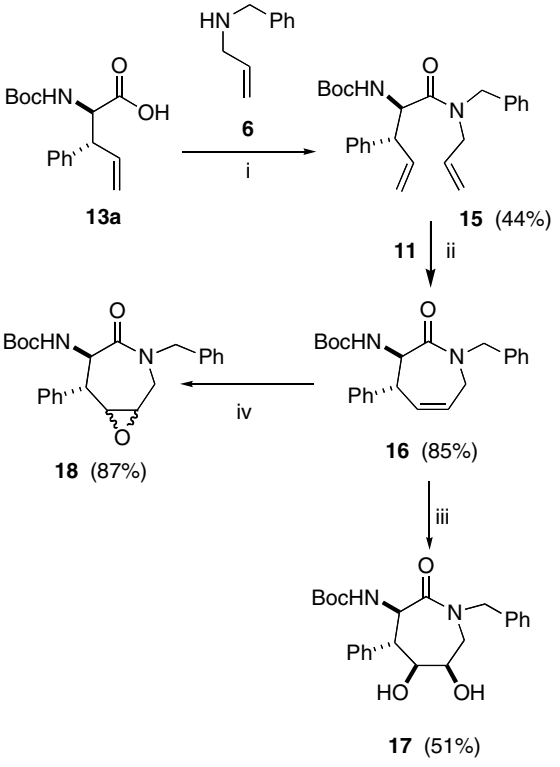


Scheme 2. Reagents and conditions: (i) (*Z*)-Cinnamyl alcohol, DCC, DMAP, CH_2Cl_2; (ii) quinine or quinidine, LHMDS, $Al(OiPr)_3$, THF, −78 °C–rt; (iii) (*S*)-Ala-OBn·HCl, EDCI, HOBT, NMP, rt, 16 h.

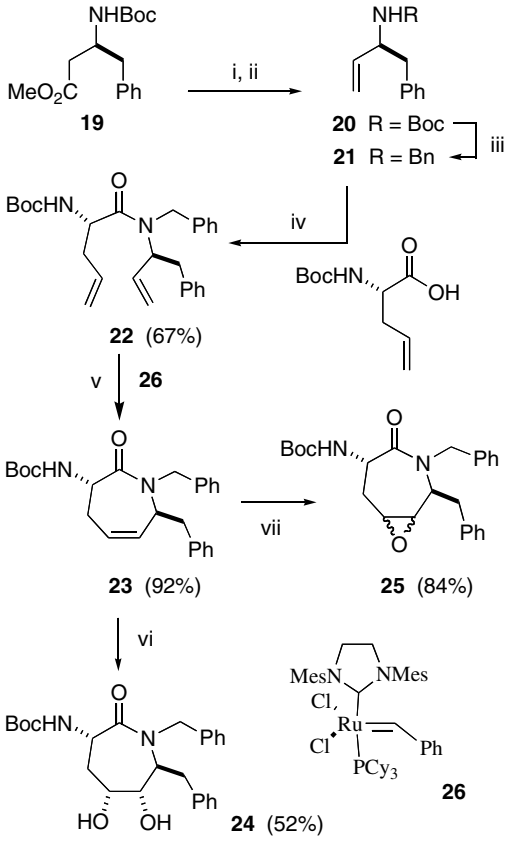
in the presence of either quinine or quinidine to give **13a** (50%) and **13b** (47%), respectively (Scheme 2). The optical purities of **13a** and **13b** were determined to be >90% and >75%, respectively, by coupling each with (*S*)-alanine benzyl ester hydrochloride, in the presence of EDCI, HOBT and NMP, and determining the ratio of **14a** and **14b** by ^{1}H NMR spectrum (Scheme 2). Isomer **13a** was used in subsequent steps of the synthesis since it was obtained in higher ee.

The olefin-substituted amino acid **13a** was coupled with *N*-allyl benzyl amine **6** in the presence of EDCI, HOBT and *N*-ethylmaleimide (NEM) to give the diene amide **15** in 44% yield (Scheme 3). The diene amide was found to be a mixture of rotamers [2:1 based on ^{1}H NMR]. The diene **15** was subjected to ring-closing metathesis using Grubb's first-generation catalyst **11**, in refluxing CH_2Cl_2, under an argon atmosphere, to give the lactam **16** in 85% yield as a single isomer as determined by ^{1}H NMR spectroscopy (Scheme 3). The olefinic lactam **16** was then derivatised as for (±)-**8** (see Scheme 3). However, in this case Sharpless AD,[12] using either $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, gave a single diastereoisomer **17** in 51% yield, along with recovered starting material **16** (36%). The configuration of the product was assigned as shown in **17** based on 2D NOE data: enhancements were observed between (i) H-4, the NH, and the C-5 and C-6 OH protons; and (ii) H-3, H-5 and the H-7 methylene. As for **9a**, the relative configuration of **17** at C-3, C-5 and C-6 is consistent with addition of osmium *syn* to the *N*-Boc group of **16** due to hydrogen bonding[13] of NH to the intermediate osmate ester (cf. reaction of (±)-**8** to give **9a** as the major product, see Scheme 1 and earlier for a discussion). However, in this case only a single isomer **17** was obtained, presumably since the configuration of the C-4 phenyl group reinforces the facial selectivity. Reaction of **16** with Oxone® and acetone/water[14] (Scheme 3) gave the epoxides **18** as a mixture (~5:4) of two diastereoisomers (determined by ^{1}H NMR), which could not be separated by crystallization or column chromatography. As such, the configuration of the diastereoisomers was not assigned.

The introduction of a substituent at C-7 of the seven-membered lactams was achieved using the substituted *N*-benzylamine **21** as starting material, itself derived from (*S*)-*N*-Boc-phenylalanine methyl ester **19** in three steps[16] (Scheme 4). In particular, DIBAL(H) reduction of **19**, in dry toluene at −78 °C, gave the corresponding aldehyde, which was immediately subjected to a Wittig olefination using $Ph_3P^+CH_3Br^-$ and potassium bis(trimethylsilyl)amide (KHMDS) to give the allyl carbamate **20** in 45% yield (Scheme 4). Benzylation of **20** with NaH and BnBr followed by removal of the Boc group with TFA gave the allyl amine **21**. This was then coupled with (*S*)-*N*-Boc-allyl glycine in the presence of ben-



Scheme 3. Reagents and conditions: (i) EDCI, HOBT, NEM, rt, 72 h; (ii) CH_2Cl_2, reflux, 24 h; (iii) $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, $K_2OsO_2(OH)_2$, K_2CO_3, $K_3(FeCN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C–rt, 48 h; (iv) Oxone®/acetone, H_2O, 0 °C–rt, 16 h.



Scheme 4. Reagents and conditions: (i) DIBALH, toluene, −78 °C; (ii) $Ph_3P^+CH_3Br^-$, KHMDS, THF, −78 °C; (iii) NaH, BnBr, DMF, 0 °C followed by TFA, CH_2Cl_2; (iv) CH_2Cl_2, BOP, DIPEA, rt, 72 h; (v) **26**, CH_2Cl_2, reflux, 36 h; (vi) $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL or no ligand, $K_2OsO_2(OH)_2$, K_2CO_3, $K_3(FeCN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C–rt, 48 h; (vii) Oxone®/acetone, H_2O, 0 °C–rt, 16 h.

zotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and diisopropylethyl amine (DIPEA), at room temperature in dry CH_2Cl_2, to give the diene **22** in 67% yield (Scheme 4). The progress of the coupling was monitored by TLC and turnover was increased with the addition of a further four equivalents of BOP in portions after every 14 h to the reaction mixture.[17]

The diene **22** was treated with Grubb's second-generation catalyst[18] **26**, in refluxing CH_2Cl_2, to give 92% of the olefinic lactam **23** (Scheme 4). The olefin of **23** was then subjected to Sharpless AD[12] using both $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL as ligands to give the same diastereoisomeric diol in each case (~52–60% yield), assigned structure **24** (Scheme 4). The absolute configuration of this diol was assigned on the basis of the known configuration of the starting materials and 2D NOE data: enhancements were observed between H3, H5, H6 and the benzylic methylene at C-7. Again, for reasons discussed earlier, diol formation occurs *syn* to the NH-Boc group, a preference reinforced by the relative configuration of the C-7 benzyl group. It is interesting to note that treatment of **23** with potassium osmate, potassium carbonate, potassium ferricyanide and methane sulfonamide in the presence of *t*-BuOH and water gave the same product **24** (59%) as a single diastereoisomer.

Reaction of **23** with Oxone® and acetone/water[14] (step vii, Scheme 4) gave the epoxides **25** as a mixture of two diastereoisomers (~1:1 as determined by ^1H NMR) in 84% yield, which could not be separated by crystallization or column chromatography. Again, the configurations of these diastereoisomers were not assigned.

2.1. Assay against HIV protease

The design of our compounds was based on known structure–activity relationship data (SAR)[9] for related cyclic ureas (e.g., **3**), cyclic sulfonamides (e.g., **4**) and some limited data on lactams of type **5**.[4a] In all these cases potency is favoured by a hydrophobic group (e.g., an aryl substituent) at the N1/C-3, and C-4/C-7 positions, the so-called P2/P2′ and P1/P1′ substituents that interact with the complementary S2/S2′ and S1/S1′ binding pockets in the protease active site (see Fig. 2 for a definition of the nomenclature). The inhibitors prepared in this paper possess a *syn* diol, rather than *anti*, as is found in most of the literature inhibitors of types **3** and **4**. However, it is important to note that the few literature examples of cyclic ureas with a *syn* diol, and the appropriate absolute configuration, are of approximately equal potency to the *anti* analogues.[19,20] As such a *syn* diol is a valid geometry to target in our system. The synthetic derivatives (±)-**9a**, (±)-**10**, **17**, **18**, **24** and **25** were assayed against HIV protease[21] and the IC_{50} values are given in Table 1.

All the inhibitors showed modest activity in the micromolar range, as might be expected given that they lack an aryl substituent at all available ring positions. Of these compounds the epoxides (**10**, **18** and **25**) are all more potent than the corresponding diols (**9a**, **17** and **24**). It is interesting to note that there are few reports of epoxide-based inhibitors of HIV protease.[9b,23] The results suggest that the absolute configuration of the inhibitors may influence activity, with the epoxide and diol inhibitors **24** and **25** (IC_{50} = 55.3 and 15.3 μM, respectively) being more potent than the corresponding diol analogues **17** and **18** (IC_{50} = 75 and 19 μM, respectively). However, it should be noted that **24**/**25** have a benzyl substituent at C-7 (P1′) while **17**/**18** have a phenyl substituent at C-4 (P1), and the observed differences in potency may reflect the relative 'fit' of these substituents in the protease binding pocket. Somewhat surprisingly, the most potent inhibitor in the series proved to be the seven-membered racemic lactam epoxide **10** (IC_{50} = 10.5 μM) which lacks both P1 and P1′ substituents. The most potent reported six-membered lactam-based inhibitor of HIV protease has a K_i of 9.4 μM.[4a]

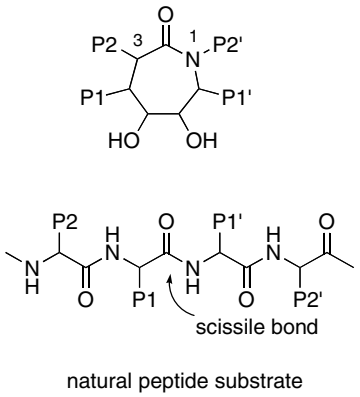


Figure 2. Comparison of cyclic HIV protease inhibitors and a natural peptide substrate depicting the P1–P*n* and P1′–P*n*′ (Schechter–Berger) nomenclature.[22]

Table 1. HIV inhibition data for the inhibitors

Compound	HIV inhibition IC_{50} (μM)
(±) **9a**	95.3
(±) **10**	10.5
17	75
18	19.3
24	55.3
25	15.7

The seven-membered lactam-based inhibitors of HIV protease reported here for the first time offer some potential advantages over related but symmetrical HIV protease inhibitors (e.g., **3**): (i) a lack of symmetry can impart improved solubility, (ii) our synthesis provides a means to incorporate a range of ring substituents to allow optimisation of interactions with the enzyme, and (iii) the Boc protecting group offers potential to incorporate these analogues into a peptide or peptide-like sequence. In essence, our seven-membered lactam-based HIV protease inhibitors provide a versatile framework for further development of inhibitors, and other lactam-based peptidomimetics. The task of introducing a fourth aryl substituent onto the ring, to give

a fully substituted analog of the literature ureas **3**, is the subject of ongoing research. By comparison, existing six-membered lactam-based HIV protease inhibitors[4a] are structurally well removed from the potent cyclic ureas and sulfonamides, difficult to prepare, and modest in activity.

3. Conclusion

Seven-membered lactam-based inhibitors of HIV protease have been prepared for the first time by ring-closing metathesis followed by hydroxylation or epoxidation of the resulting alkene. Dihydroxylation has been shown to occur *syn* to a *tert*-butylcarbamate substituent that is positioned β to the reacting olefin. Substituents at C-4 and C-7 substituents with appropriate stereochemistry enhance this *syn*-stereoselectivity. The epoxides are more potent inhibitors of HIV-1 protease than the corresponding diols.

4. Experimental

4.1. General experimental methods

^{1}H NMR spectra were recorded on a Varian Inova spectrometer (operating at 500 MHz) and ^{13}C NMR spectra on a Varian Unity 300 (operating at 75 MHz) at 23 °C in $CDCl_3$ (unless otherwise stated). Spectra were referenced relative to internal TMS (assigned 0 ppm). Optical rotations were measured on a Perkin-Elmer polarimeter model 341 with a 10 mm path length. The $[\alpha]_D^{25}$ values are reported in units deg cm^2 g^{-1}, with concentration given in 10^{-1} g cm^{-3}. IR spectra were recorded on a Shimadzu 8201PC series FTIR spectrophotometer. IR spectra were obtained neat on either KBr disc or in solid KBr. All reactions were carried out in oven-dried glassware under an argon atmosphere. CH_2Cl_2 was distilled from CaH_2. DMF was dried over P_2O_5 and distilled from CaH_2 under reduced pressure. The acids **13a**–**b**,[15] amine **21**[16] and *N*-allyl benzyl amine **6**[10] were prepared by literature methods.

4.2. General procedure A: amide bond formation

EDCI (or DCC, 1 equiv), HOBT (2 equiv) and base (3.0 equiv) were added to a solution of the acid (1.0 equiv) and amine (1.0 equiv) in dry solvent (DMF or CH_2Cl_2) under an argon atmosphere with stirring at room temperature. After stirring for 16–72 h, the solution was diluted with water and ethyl acetate (10 mL), the organic phase separated and the aqueous phase was back-extracted with ethyl acetate (3×). The combined organic fractions were washed successively with H_2O, $NaHCO_3$ soln (aq), brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude diene which was purified by column chromatography.

4.3. General procedure B: ring-closing metathesis

The catalyst (either **11** or **26**, 0.08 equiv), dissolved in dry degassed CH_2Cl_2, was added to a solution of the diene (1.0 equiv) in dry degassed CH_2Cl_2 under argon. The solution was refluxed for 24–36 h. Excess water was added, the organic layer was separated and the aqueous layer was back-extracted with CH_2Cl_2 (3×). The combined organic phases were washed with brine, evaporated under reduced pressure and the crude residue was purified by flash column chromatography.

4.4. General procedure C: diol preparation

Potassium osmate (0.05 equiv) was added to a heterogeneous slurry of the olefinic lactam (1 equiv), *t*-BuOH (3 mL), water (3 mL), potassium carbonate (3 equiv), potassium ferricyanide (3 equiv), ligand $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL (0.05 equiv) and methane sulfonamide (2 equiv) under argon and cooled in an ice bath. The mixture was warmed to room temperature slowly and after stirring for 48 h, the mixture was again cooled in an ice bath. Sodium sulfite was added and the mixture was allowed to warm to room temperature with stirring over 1–2 h. Ethyl acetate was added, the organic layer was separated, and the aqueous phase was further extracted with ethyl acetate. The combined organic fractions were washed with 2 N KOH (aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude diol which was purified by flash column chromatography.

4.5. General procedure D: epoxide formation

To a solution of the olefinic lactam (1 equiv) in acetone (12 mL) and water (10 mL) was added sodium hydrogen carbonate (34 equiv). The mixture was stirred vigorously for 15 min at room temperature, cooled in an ice bath, and Oxone® (10 equiv) was added in portions over 5 min. The resulting mixture was vigorously stirred at this temperature for 2 h and then at room temperature for 16 h. The acetone was removed under reduced pressure, ethyl acetate and water were added and the organic layer was separated, and the aqueous layer was back-extracted with ethyl acetate (3×). The combined organic fractions were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography.

4.5.1. (±)-*tert*-Butyl(1-{[allyl(benzyl)amino]carbonyl}but-3-en-1-yl) carbamate (7). A solution of EDCI (1.11 g, 5.80 mmol), HOBT (1.57 g, 11.61 mmol), NMP (1.67 mL, 17.42 mmol), (±)-*N*-Boc allylglycine (1.248 g, 5.80 mmol) and *N*-allylbenzyl amine **6** (795 mg, 5.80 mmol) in DMF (30 mL) was stirred at room temperature for 16 h according to the general procedure A. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 9:1–7:3) to give 1.77 g (88%) of (±)-**7** as a cream solid (2:5 mixture of rotamers by ^{1}H NMR). Data for mixture: ν_{max} cm^{-1} (solid KBr) 1645, 1655. ^{1}H NMR δ 1.42 (s, 9H, *t*-Bu, minor), 1.44 (s, 9H, *t*-Bu, major), 2.31–2.54 (m, 2H, CHC**H**$_2$), 3.89–4.08 (m, 2H, NC**H**$_2$), 4.48–4.75 (m, 3H, C**H**$_2$Ph and NC**H**), 5.07–5.21 (m, 4H, =C**H**$_2$), 5.67–5.81 (m, 2H, =C**H**), 7.19–7.36 (m, 5H, Ar**H**). ^{13}C NMR δ 28.3, 37.7 (minor), 37.8 (major), 47.9 (minor), 48.2 (major), 49.0 (major), 49.8 (major), 49.9 (minor),

50.1 (minor), 79.5, 117.6 (major), 117.7 (minor), 118.6, 126.8, 127.4, 127.7, 128.0, 128.5, 128.8, 132.3 (minor), 132.5 (major), 132.7 (minor), 132.8 (major), 136.2, 136.9, 155.1 (minor), 155.2 (major), 172.0 (minor), 172.2, (major). TOF MS ES$^+$ [MH]$^+$: Found: 345.2178; Calcd for $C_{20}H_{29}N_2O_3$: 345.2178.

4.5.2. (±)-*tert*-Butyl(1-benzyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl) carbamate (8). Catalyst **11** (16 mg, 0.02 mmol), dissolved in dry degassed CH_2Cl_2 (3 mL), was added to a solution of the diene (±)-**7** (95 mg, 0.25 mmol), in dry degassed CH_2Cl_2 (20 mL) under argon, according to the general procedure B. The mixture was refluxed for 24 h. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 9:1 then 8:2) to give 66 mg (76%) of (±)-**8** as a brown solid. ν_{max} cm^{-1} (solid KBr) 1647. ^{1}H NMR δ 1.38 (s, 9H, *t*-Bu), 2.20 (m, 1H, CHC**H**$_{AB}$), 2.60 (dd, 1H, J = 18 Hz, 4 Hz, CHC**H**$_{AB}$), 3.27 (dd, 1H, J = 7.5 Hz, 17.5 Hz, NC**H**$_{AB}$CH), 4.21 (td, 1H, J = 17.5 Hz, 3 Hz, NC**H**$_{AB}$CH), 4.51–4.64 (m, 2H, NC**H**$_2$Ph), 4.86–4.91 (m, 1H, C**H**NH), 5.52–5.64 (m, 2H, =C**H**), 5.82 (bd, 1H, J = 7 Hz, **NH**), 7.12–7.24 (m, 5H, Ar**H**). ^{13}C NMR δ 28.3, 33.3, 45.1, 49.9, 51.4, 79.4, 124.1, 127.4, 127.7, 128.5, 130.0, 136.7, 154.9, 172.4. TOFMS ES$^+$ [MH]$^+$: Found: 317.2242; Calcd for $C_{18}H_{25}N_2O_3$: 317.1856.

4.5.3. (3*R,5*S**,6*R**)- and (3*R**,5*R**,6*S**)-*tert*-Butyl [1-benzyl-5,6-dihydroxy-2-oxoazepan-3-yl] carbama-te (9a) and (9b).** A mixture of potassium osmate (3 mg, 0.01 mmol), olefinic lactam (±)-**8** (52 mg, 0.16 mmol), *t*-BuOH (3 mL), water (3 mL), potassium carbonate (68 mg, 0.49 mmol), potassium ferricyanide (162 mg, 0.49 mmol), ligand $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL (6.4 mg, 0.002 mmol) and methane sulfonamide (31 mg, 0.33 mmol) was reacted according to the general method C. The crude product, obtained as a mixture, was purified by flash column chromatography (petroleum ether/ethyl acetate/acetone = 5:1:4) to give 41 mg (71%) of a mixture of (±)-**9a** and (±)-**9 b** (9:1 by ^{1}H NMR). Recrystallization ($CHCl_3$/petroleum ether) gave the major isomer (±)-**9a** as a white solid and (±)-**9b** as a mixture with (±)-**9a**. Data for major isomer (±)-**9a**. ν_{max} cm^{-1} (solid KBr) 3417, 2977, 1701, 1652. ^{1}H NMR (CD_3CN) δ 1.23 (s, 9H, *t*-Bu), 1.53 (m, 1H, CHC**H**$_{AB}$), 1.67 (dd, 1H, J = 12.5 Hz, 4.0 Hz, CHC**H**$_{AB}$), 2.94 (d, 1H, J = 4 Hz, NCH$_2$CHO**H**), 3.04 (d, 1H, J = 5.0 Hz, CHCH$_2$CHO**H**), 3.14 (dd, 1H, J = 15.5 Hz, 6 Hz, NC**H**$_{AB}$), 3.23–3.26 (m, 1H, NC**H**$_{AB}$), 3.54 (bm, 1H, CHCH$_2$C**H**), 3.65 (br s, 1H, NCH$_2$C**H**), 3.71 (d, 1H, J = 15.0 Hz, NC**H**$_{AB}$Ph), 4.01–4.05 (m, 1H, C**H**), 5.16 (d, 1H, J = 15 Hz, NC**H**$_{AB}$Ph), 5.72 (br s, 1H, N**H**), 7.03–7.14 (m, 5H, Ar**H**). ^{13}C NMR δ 28.4, 34.6, 46.9, 49.0, 53.1, 68.4, 72.3, 79.9, 127.6, 128.1, 128.7, 136.9, 155.2, 171.6. TOFMS ES$^+$ [MH]$^+$: Found: 351.1922; Calcd for $C_{18}H_{27}N_2O_5$: 351.1920. Data for (±)-**9b** from mixture: ^{1}H NMR δ 1.44 (s, 9H, *t*-Bu), 1.83 (t, 1H, J = 12.5 Hz, CHC**H**$_{AB}$), 2.23–2.35 (m, 1H, CHC**H**$_{AB}$), 2.92–3.09 (m, 2H, NC**H**$_2$), 3.31–3.34 (m, 1H, NCH$_2$CHO**H**), 4.12 (br s, 1H, CHCH$_2$CHO**H**), 4.48 (d, 1H, J = 15.0 Hz, NC**H**$_{AB}$Ph), 4.75 (d, 1H, J = 14.5 Hz, NC**H**$_{AB}$Ph), 4.84–4.87 (m, 1H, NHC**H**), 6.06 (bd, 1H, J = 5.5 Hz, N**H**), 7.16–7.34 (m, 5H, Ar**H**). ^{13}C NMR δ 28.3, 38.7, 46.1, 51.7, 68.1, 68.4, 69.9, 79.9, 127.8, 128.2, 128.7, 136.6, 167.8, 172.7.

4.5.4. (±)-*tert*-Butyl(3-benzyl-4-oxo-8-oxa-3-azabicyco-[5,1,0]oct-5-yl]) carbamate (10). The olefinic lactam (±)-**8** (138 mg, 0.44 mmol) in acetone (12 mL) and water (10 mL) was treated with sodium hydrogen carbonate (1.24 g, 14.80 mmol) and Oxone® (2.68 g, 4.35 mmol) as described in the general procedure D. The resulting crude epoxide was purified by column chromatography (petroleum ether/ethyl acetate = 7:3) to give 91 mg (63%) of (±)-**10** as a white solid (1:1 by ^{1}H NMR). Data from mixture: ν_{max} cm^{-1} (solid KBr) 1652. ^{1}H NMR δ 1.45 (s, 9H), 1.91 (t, 0.5H J = 12.5 Hz), 2.03 (t, 0.5H, J = 12.5 Hz), 2.50–2.81 (m, 0.5H), 2.65 (dd, 0.5H, J = 14.5, 2.5 Hz), 2.90 (dd, 0.5H, J = 11, 6 Hz), 3.01–3.06 (m, 1H), 3.18 (t, 0.5H, J = 5.5 Hz), 3.59–3.67 (m, 1.5H), 3.92 (d, 0.5H, J = 15.5 Hz), 3.96 (d, 0.5H, J = 17 Hz), 4.33 (d, 0.5H, J = 14.5 Hz), 4.40–4.43 (m, 0.5H), 4.55–4.59 (m, 0.5H), 4.95 (d, 0.5H, J = 14.5 Hz), 5.27 (d, 0.5H, J = 15 Hz), 5.73 (bd, 0.5H, J = 7 Hz), 5.86 (bd, 0.5 H, J = 6.5 Hz), 7.21–7.35 (m, 10H). ^{13}C NMR δ 28.3, 30.4, 31.3, 44.2, 47.2, 47.7, 48.3, 50.0, 51.1, 51.2, 52.2, 52.4, 52.7, 79.6, 79.7, 127.6, 127.8, 128.0, 128.2, 128.6, 128.8, 136.2, 136.8, 154.8, 154.9, 171.3, 172.2; TOFMS ES$^+$ [MH]$^+$: Found: 333.1811; Calcd for $C_{18}H_{25}N_2O_4$: 333.1814.

4.5.5. (*S*)-Benzyl-2-[(2*R*,3*R*)-2-(*tert*-butyloxycarbonyl)-3-phenylpent-4-enamido]propanoate (14a). EDCI (66 mg, 0.34 mmol), HOBT (92 mg, 0.68 mmol) and NMP (10 μL, 1.03 mmol) were added to a solution of the acid **13a** (100 mg, 0.34 mmol) and (*S*)-alanine benzyl ester hydrochloride (73 mg, 0.34 mmol), according to general procedure A. Crude **14a** (containing <10% of a second diastereoisomer tentatively assigned **14b**) was purified by column chromatography (petroleum ether/ethyl acetate = 8.5:1.5) to give 90 mg (58%) of **14a** as a white solid. ^{1}H NMR δ 1.30 (d, 3H, J = 7 Hz, C**H**$_3$), 1.39 (s, 9H, *t*-Bu), 3.98 (t, 1H, J = 6.5 Hz, PhC**H**), 4.46 (m, 1H, CHC**H**), 4.51–4.56 (m, 1H, CH$_3$C**H**), 4.96 (bd, 1H, J = 6 Hz, N**H**), 5.14–5.19 (m, 4H, =C**H**$_2$, CO$_2$C**H**$_2$), 6.04–6.11 (m, 1H, =C**H**), 6.26 (d, 1H, J = 7.5 Hz, N**H**), 7.22–7.39 (m, 10H, Ar**H**). ^{13}C NMR δ 18.3, 28.2, 48.2, 51.1, 58.2, 67.1, 80.2, 118.1, 127.2, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 130.9, 136.0, 139.1, 155.3, 169.8, 172.2; TOFMS ES$^+$ [MH]$^+$: Found: 451.2437; Calcd for $C_{27}H_{35}N_2O_4$: 451.2597.

4.5.6. *tert*-Butyl(1*R*,2*R*)-1-{[allyl(benzyl)amino]carbonyl}-2-phenylbut-3-en-1-yl] carbamate (15). EDCI (200 mg, 1.03 mmol), HOBT (334 mg, 2.47 mmol), NEM (258 mg, 2.06 mmol), *N*-allyl benzyl amine **6** (2.06 mg, 5.80 mmol) and **13a** (300 mg, 1.03 mmol) in CH_2Cl_2 (30 mL) were reacted for 72 h according to general procedure A. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 9:1–8.5:1.5) to give 183 mg (44%) of the desired diene **15** as a white solid (2:1 mixture of rotamers by ^{1}H NMR). Data for mixture: ν_{max} cm^{-1} (solid KBr) 1697, 1647. ^{1}H NMR δ 1.28 (s, 9H, *t*-Bu, minor), 1.30 (s, 9H, *t*-Bu, major), 3.66–4.21 (m, 3H, PhC**H**,

NC**H**$_2$), 4.33–4.78 (m, 2H, NC**H**$_2$Ph), 4.92–5.04 (m, 1H, NHC**H**), 5.08–5.20 (m, 4H, =C**H**$_2$) 5.63–5.77 (m, 1H, =C**H**), 5.92–6.13 (m, 1H, =C**H**), 7.16–7.34 (m, 10H, Ar**H**). ^{13}C NMR δ 28.1 (major), 28.3 (minor), 47.9 (minor), 48.3 (major), 49.2 (major), 50.0 (minor), 53.1 (major), 53.2 (minor), 53.7 (major), 53.7 (minor), 79.6 (major and minor), 117.7 (minor), 117.9 (major), 126.9, 127.2, 127.4, 127.6, 128.4, 128.5, 128.6 (major and minor), 132.4 (major), 132.7 (major), 136.3 (minor), 136.6 (minor), 136.7 (major), 136.9 (minor), 139.3 (major), 139.4 (minor), 154.7 (minor), 154.8 (major), 171.3 (minor), 171.5 (major); $[\alpha]_D^{20}$ +50.0 (*c* 1.0, $CHCl_3$); TOFMS ES$^+$ [MH]$^+$: Found: 421.2498; Calcd for $C_{26}H_{33}N_2O_3$: 421.2491.

4.5.7. *tert*-Butyl[(3*R*,4*R*)-1-benzyl-4-phenyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl] carbamate (16). Catalyst **11** (68.5 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) was reacted with **15** (175 mg, 0.42 mmol), in CH_2Cl_2 (20 mL) according to the general procedure B. The mixture was refluxed for 24 h and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 4:1) to give 139 mg (85%) of **16** as a white crystalline solid. ν_{max} cm^{-1} (solid KBr) 1641. ^{1}H NMR δ 1.10 (s, 9H, *t*-Bu), 3.33–3.42 (m, 2H, PhC**H**, NC**H**$_{AB}$), 4.45 (d, 1H, *J* = 17 Hz, NC**H**$_{AB}$), 4.62 (s, 2H, NC**H**$_2$Ph), 5.16 (t, 1H, *J* = 10.5 Hz, **CH**), 5.41 (bd, 1H, *J* = 9 Hz, N**H**), 5.64–5.67 (m, 1H, =CH), 5.70–5.74 (m, 1H, =CH), 7.12–7.27 (m, 10H, Ar**H**). ^{13}C NMR δ 27.8, 44.6, 49.4, 51.4, 53.7, 79.0, 124.4, 126.9, 127.5, 127.9, 128.1, 128.6, 129.2, 134.5, 136.6, 140.1, 154.6, 172.1; TOFMS ES$^+$ [MH]$^+$: Found: 393.2204; Calcd for $C_{24}H_{29}N_2O_3$: 393.2178.

4.5.8. *tert*-Butyl[(3*R*,4*R*,5*S*,6*R*)-1-benzyl-5,6-dihydroxy-4-phenyl-2-oxoazepan-3-yl] carbamate (17). Potassium osmate (2.2 mg, 0.003 mmol), olefinic lactam **16** (25 mg, 0.06 mmol), *t*-BuOH (3 mL), water (3 mL), potassium carbonate (26 mg, 0.19 mmol), potassium ferricyanide (63 mg, 0.19), ligand $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL (2.5 mg, 0.0003 mmol) and methane sulfonamide (12 mg, 0.13 mmol) were reacted according to the general method C with stirring for 48 h. The crude product (single isomer by ^{1}H NMR) was purified by flash column chromatography (petroleum ether/ethyl acetate = 1:1–1:4) to give 14 mg (51%) of **17** as a colourless oil, along with 9 mg (36%) of recovered **16**. Data for **17**: ν_{max} cm^{-1} (KBr disc) 3417, 2977, 1701, 1654. ^{1}H NMR δ 1.21 (s, 9H, *t*-Bu), 1.70 (br s, 1H, CH_2CHO**H**), 1.90 (br s, 0.5 H, CHCHO**H**), 2.74 (br s, 0.5 H, CHCHO**H**), 3.09 (t, 1H, *J* = 10 Hz, C**H**Ph), 3.56 (dd, 1H, *J* = 16.5 Hz, 6.0 Hz, NC**H**$_{AB}$CH), 3.62–3.68 (m, 1H, NC**H**$_{AB}$CH), 4.02 (d, 1H, *J* = 15 Hz, NC**H**$_{AB}$Ph), 4.07 (dd, 1H, *J* = 11, 3.5 Hz, PhCHC**H**), 4.15–4.17 (m, 1 H, CH_2C**H**), 4.76 (t, 1 H, *J* = 9.5 Hz, NHC**H**), 5.43 (d, 1H, *J* = 9 Hz, N**H**), 5.59 (d, 1H, *J* = 14.5 Hz, NC**H**$_{AB}$Ph), 7.27–7.36 (m, 10 H, Ar**H**). ^{13}C NMR δ 28.1, 46.4, 49.8, 51.3, 53.0, 68.5, 76.7, 79.3, 127.6, 127.8, 128.2, 128.7, 128.7, 136.6, 136.9, 155.1, 171.8; TOFMS ES$^+$ [MH]$^+$: Found: 427.2309; Calcd for $C_{24}H_{31}N_2O_5$: 427.2233. Data for **16** as above.

4.5.9. *tert*-Butyl[(1*S,5*R*,6*R*,7*R**)-3-benzyl-6-phenyl-4-oxo-8-oxa-3-azabicyclo-[5.1.0]oct-5-yl]carbamate (18).** The olefinic lactam **16** (40 mg, 0.10 mmol) in acetone (6 mL) and water (5 mL) was treated with sodium hydrogen carbonate (291 mg, 3.46 mmol) and Oxone® (627 mg, 1.02 mmol) as described in the general procedure D. The resulting crude epoxide was purified by column chromatography (petroleum ether/ethyl acetate = 7:3) to give 36 mg (87%) of **18** (5:4 mixture by ^{1}H NMR) as a white solid. Data for mixture: ν_{max} cm^{-1} (solid KBr) 1654. ^{1}H NMR δ 1.16 (s, 9H, *t*-Bu, major), 1.26 (s, 9H, *t*-Bu, minor), 3.00–3.28 (m, 3H), 3.69–3.76 (m, 1H), 3.92-4.01 (m), 3.98–4.36 (m), 4.22 (d, *J* = 16.5 Hz), 4.34 (d, *J* = 15 Hz), 4.82–4.90 (m, 1H), 5.05 (d, *J* = 14 Hz), 5.24 (d, 1H, *J* = 10 Hz), 5.33 (d, *J* = 15.5 Hz), 5.41 (d, 1H, *J* = 9 Hz), 7.26–7.53 (m, 10H). ^{13}C NMR δ 28.0, 29.7, 43.9, 47.3, 47.6, 50.4, 51.3, 52.1, 52.2, 54.5, 56.4, 57.0, 68.4, 79.3, 80.4, 127.3, 127.7, 128.5, 128.7, 129.0, 129.6, 136.2, 136.9, 139.3, 154.6, 155.2, 169.4, 171.4. TOFMS ES$^+$ [M+H]$^+$: Found: 409.2124; Calcd for $C_{24}H_{29}N_2O_4$: 409.2127.

4.5.10. *tert*-Butyl (1*S*)-1-({benzyl[(1*S*)-1-benzylprop-2-en-1-yl]amino}carbonyl)but-3-en-1-yl carbamate (22). (*S*)-*N*-Boc allyl glycine (250 mg, 1.16 mmol), BOP[24] (513 mg, 1.16 mmol) and DIPEA (620 μL, 3.48 mmol) were added to a solution of **21**[16] (275 mg, 1.16 mmol) in CH_2Cl_2 (20 mL) under argon with stirring at room temperature for 72 h. Four additional equivalents of BOP were added in portions to the reaction mixture to increase the turnover of the reaction.[17] The solution was diluted with water and ethyl acetate (10 mL), organic layer was separated and aqueous layer back-extracted with ethyl acetate (3×). The combined organic fractions were washed successively with H_2O, $NaHCO_3$ soln (aq), brine and dried ($MgSO_4$). Evaporation under reduced pressure and flash column chromatography (petroleum ether/ethyl acetate = 9:1) gave 336 mg (67%) of **22** as a clear oil (3:2 mixture of rotamers by ^{1}H NMR). Data for mixture: ν_{max} cm^{-1} (KBr disc) 1647, 1633. ^{1}H NMR δ 1.42 (s, 9H, *t*-Bu, major), 1.43 (s, 9H, *t*-Bu, minor), 1.96–2.21 (m, 2H, CHC**H**$_{AB}$, CHC**H**$_{AB}$Ph), 2.72–3.12 (m, 2H, CHC**H**$_{AB}$, CHC**H**$_{AB}$Ph), 4.26–4.51 (m, 2H, CHC**H**$_{AB}$Ph, NC**H**$_{AB}$Ph,), 4.51–4.87 (m, NC**H**$_{AB}$Ph, NHC**H**), 4.95–5.31 (m, =C**H**$_2$, NC**H**$_{AB}$Ph), 5.53–6.01 (m, 2H, =CH), 7.05–7.29 (m, 10H, Ar**H**). ^{13}C NMR δ 28.3 (major), 29.6 (minor), 37.3 (minor), 37.6 (major), 38.4 (major), 38.6 (minor), 46.5 (minor), 49.7 (major), 49.7 (minor), 50.7 (major), 60.9 (major), 61.1 (minor), 79.5 (major), 79.6 (minor), 117.6 (minor), 118.0 (major), 118.1 (minor), 118.2 (major), 126.4, 126.7, 126.8, 127.0, 127.3, 27.5, 128.3, 128.6, 128.7, 129.3 (major and minor), 133.0 (major), 133.2 (minor), 135.7 (major), 136.2 (minor), 137.1 (major), 137.4 (minor), 138.1 (major), 138.4 (minor), 155.1 (major), 155.2 (minor), 172.7 (major), 172.9 (minor); $[\alpha]_D^{20}$ −66.2 (*c* 1.0, $CHCl_3$); TOFMS ES$^+$ [MH]$^+$: Found: 435.2635; Calcd for $C_{27}H_{35}N_2O_3$: 435.264.

4.5.11. *tert*-Butyl[(3*S*,7*S*)-1-benzyl-7-benzyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl] carbamate (23). Catalyst **26** (46 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) was reacted with **22** (291 mg, 0.67 mmol) in CH_2Cl_2 (20 mL)

according to the general procedure B. The mixture was refluxed for 36 h and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 9:1 then 4:1) to give 250 mg (92%) of **23** as a brown oil. ν_{max} cm^{-1} (KBr disc) 1649. ^1H NMR δ 1.48 (s, 9H, *t*-Bu), 2.30 (dt, 1H, $J = 14.5$, 2 Hz, $CHCH_{AB}$), 2.66 (dd, 1H, $J = 18$, 4 Hz, $CHCH_{AB}$), 3.03–3.11 (m, 2H, $CHCH_2Ph$), 3.56 (d, 1H, $J = 15.5$ Hz, $NCH_{AB}Ph$), 3.92 (dd, 1H, $J = 14$ Hz, 6.5 Hz, $CHCH_2Ph$), 4.82–4.86 (m, 1H, NHCH), 5.07 (d, 1H, $J = 15$ Hz, $NCH_{AB}Ph$), 5.46 (t, $J = 10$ Hz, 1H, NCHCH), 5.77 (dd, 1H, $J = 11.5$, 6 Hz, $CHCH_2CH$), 6.03 (bd, 1H, $J = 6.5$ Hz, NH), 7.09–7.35 (m, 10H, ArH). ^{13}C NMR δ 28.4, 32.5, 42.4, 52.3, 52.4, 61.4, 79.5, 126.9, 127.4, 127.4, 127.5, 128.2, 128.6, 128.6, 129.1, 136.9, 137.5, 155.1, 172.1; $[\alpha]_D^{20}$ −29.8 (*c* 1.0, $CHCl_3$); TOFMS ES$^+$ $[MH]^+$: Found: 429.2157; Calcd for $C_{25}H_{31}N_2NaO_3$: 429.2154.

4.5.12. *tert*-Butyl[(3*S*,5*R*,6*S*,7*S*)-1-benzyl-5,6-dihydroxy-7-benzyl-2-oxoazepan-3-yl] carbamate (24). *Method A*: potassium osmate (2 mg, 0.005 mmol), **23** (20 mg, 0.05 mmol), *t*-BuOH (3 mL), water (3 mL), potassium carbonate (21 mg, 0.15 mmol), potassium ferricyanide (49 mg, 0.15), ligand $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL (4 mg, 0.002 mmol) and methane sulfonamide (10 mg, 0.1 mmol) were reacted according to general method C with stirring for 48 h. The crude product (obtained as a single diastereoisomer, based on ^1H NMR) was purified by flash column chromatography (petroleum ether/ethyl acetate = 1:1–1:4) to give 11 mg (52%) of **24** as a white oily solid. ν_{max} cm^{-1} (solid KBr) 3423, 2977, 1701, 1685. ^1H NMR (CD_3CN) δ 1.30 (s, 9H, *t*-Bu), 1.64–1.74 (m, 2H, $CHCH_2$), 2.49 (dd, $J = 13.5$, 6 Hz, 1H, $CHCH_{AB}Ph$), 2.76 (br s, 1H, CHCHOH), 2.86 (dd, 1H, $J = 13.5$, 10 Hz, $CHCH_{AB}Ph$), 2.99 (br s, 1H, CH_2CHOH), 3.51 (br s, 1H, CHCHOH), 3.61–3.66 (m, 1H, CHCH), 3.96 (d, 1H, $J = 14.5$ Hz, $NCH_{AB}Ph$), 4.01–4.03 (m, 1H, CH_2CHOH), 4.15–4.18 (m, 1H, $CHCH_2CH$), 4.69 (d, 1H, $J = 14.5$ Hz, $NCH_{AB}Ph$), 5.82 (br s, 1H, NH), 6.76–7.09 (m, 5 H, ArH), 7.13–7.19 (m, 5H, ArH). ^{13}C NMR δ 28.4, 33.9, 37.2, 50.0, 54.8, 63.4, 68.6, 69.7, 79.8, 127.0, 128.0, 128.55, 128.79, 128.8, 129.2, 137.1, 137.3, 155.2, 171.4; $[\alpha]_D^{20}$ +18.1 (*c* 1.0, $CHCl_3$). TOFMS ES$^+$ $[MH]^+$: Found: 441.2389; Calcd for $C_{25}H_{33}N_2O_5$: 441.2389. *Method B*: potassium osmate (2 mg, 0.005 mmol), olefinic lactam **23** (20 mg, 0.05 mmol), *t*-BuOH (3 mL), water (3 mL), potassium carbonate (21 mg, 0.15 mmol), potassium ferricyanide (49 mg, 0.15) and methane sulfonamide (10 mg, 0.1 mmol) were reacted according to general method C in the absence of ligand with stirring for 48 h. The crude product **24** (obtained as a single diastereoisomer, based on ^1H NMR) was purified by flash column chromatography (petroleum ether/ethyl acetate = 1:1–1:4) to give 12.5 mg (59%) of **24** as a white oily solid. Data as above.

4.5.13. *tert*-Butyl[(1*S,2*S*,5*S*,7*R**)-2,3-dibenzyl-4-oxo-8-oxa-3-azabicyclo[5,1,0]oct-5-yl] carbamate (25).** A solution of **23** (80 mg, 0.20 mmol) in acetone (12 mL) and water (10 mL) was treated with sodium hydrogen carbonate (562 mg, 6.70 mmol) and Oxone® (1.21 g, 1.97 mmol) as described in general procedure D. The resulting crude epoxide (~1:1, based on ^1H NMR) was purified by column chromatography (petroleum ether/ethyl acetate = 7:3) to give 70 mg (84%) of **25** as a white foam (~1:1 mixture of diastereoisomers by ^1H NMR). Data for mixture: ν_{max} cm^{-1} (solid KBr) 1645. ^1H NMR δ 1.45 (s, 9H), 2.00–2.10 (m, 1H), 2.55 (m, 0.5H), 2.69 (d, $J = 14.5$ Hz, 0.5H), 2.89–2.98 (m, 1.5H), 3.11–3.20 (m, 1H), 3.27–3.32 (m, 1.5H), 3.63 (d, 0.5H, $J = 14.5$ Hz), 3.92 (dd, 0.5H, $J = 14.5$, 7 Hz), 4.11 (m, 0.5H), 4.40 (s, 1H), 4.55–4.65 (m, 1H), 5.05 (d, 0.5H, $J = 15$ Hz,), 5.79 (bd, $J = 6.5$ Hz, 0.5H), 5.97 (bd, $J = 6.5$ Hz, 0.5H), 6.92 (d, $J = 7.5$ Hz, 1H), 7.14–7.36 (m, 9H). ^{13}C NMR δ 28.4, 29.8, 32.2, 37.5, 38.6, 46.9, 50.6, 52.4, 53.1, 53.3, 53.7, 54.8, 55.3, 58.8, 58.9, 79.8, 80.4, 126.9, 127.1, 127.8, 127.9, 128.5, 128.7, 128.9, 129.0, 129.3, 136.2, 137.0, 137.2, 137.5, 155.0, 171.2, 172.2. TOFMS ES$^+$ $[MH]^+$: Found: 423.2284; Calcd for $C_{25}H_{31}N_2O_4$: 423.2284.

Acknowledgments

The work was supported by a Royal Society of New Zealand Marsden grant. The authors also thank Professor Fabio Benedetti (Department of Chemical Sciences Trieste, Italy) for assistance with the HIV-I protease inhibition assay.

References and notes

1. Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125; Ghosh, A.; Koltun, E.; Bilcer, G. *Synthesis* **2001**, 1281; Kidwai, M.; Sapra, P.; Bhushan, K. R. *Curr. Med. Chem.* **1999**, *6*, 195.
2. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004**, *67*, 1216; Groweiss, A.; Newcomer, J. J.; O' Keefe, B. R.; Blackman, A.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 1691.
3. Velten, R.; Erdelen, C.; Gehling, M.; Göhrt, A.; Gondol, D.; Lenz, J.; Lockhoff, O.; Wachendorff, U.; Wendisch, D. *Tetrahedron Lett.* **1998**, *39*, 1737.
4. (a) De Lucca, G. V. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 501; (b) Battisini, L.; Rassu, G.; Pinna, L.; Zanardi, F.; Casiraghi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 765; (c) Humphries, M. E.; Murphy, J.; Phillips, A. J.; Abell, A. D. *J. Org. Chem.* **2003**, *68*, 2432.
5. Hoog, S. S.; Zhao, B.; Winborne, E.; Fisher, S.; Green, D. W.; DesJarlais, R. L.; Newlander, K. A.; Callahan, J. F.; Moore, M. L.; Huffman, W. F. *J. Med. Chem.* **1995**, *38*, 3246.
6. For lactamizations, see: Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671; Rico, I.; Halvorsen, K.; Dubrule, C.; Lattes, A. *J. Org. Chem.* **1994**, *59*, 415; Huang, W.; Kalivretenos, A. G. *Tetrahedron Lett.* **1995**, *36*, 9113.
7. Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606; Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677; Belvisi, L.; Colombo, L.; Manzoni, L.; Potenza, D.; Scolastico, C. *Synlett* **2004**, *9*, 1449.
8. Aitken, S. G.; Abell, A. D. *Aust. J. Chem.* **2005**, *58*, 1; Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.
9. (a) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; DeLucca, G. V.; Eyermann, C. J.; Chang, C.-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P.

N.; McHugh, R. J.; Han, Q.; Li, R.; Markwalder, J. A.; Seitz, S. P.; Sharpe, T. R.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winslow, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. *J. Med. Chem.* **1996**, *39*, 3514; (b) Lam, Y. P.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; De Lucca, G. V. Rodgers, J. D. US Patent 5, 610, 294, issued March 11, 1997; (c) Jun, J. H.; Dougherty, J. M.; Jimenez, M del. S.; Hanson, P. R. *Tetrahedron* **2003**, *59*, 8901; (d) Ax, A.; Schaal, W.; Vrang, L.; Samuelsson, B.; Hallberg, A.; Karlén, A. *Bioorg. Med. Chem.* **2005**, *13*, 755; (e) McReynolds, M. D.; Sprott, K. T.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 4673.

10. Mustapha, K.; Michel, P. C.; Marie, J. S. *Bull. Chim. Soc. Fr.* **1981**, *11*, 449.
11. Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858.
12. Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 6895; Wang, L.; Sharpless, K. B. *J. Org. Chem.* **1992**, *114*, 7568.
13. Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. J. *Org. Biomol. Chem.* **2003**, *1*, 2173.
14. Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
15. Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113.
16. Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.
17. Albericio, F.; Bofill, J. M.; El-Faham, A.; Kates, S. A. *J. Org. Chem.* **1998**, *63*, 9678.
18. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
19. Kaltenbach, R. F., III; Nugiel, D. A.; Lam, P. Y. S.; Klabe, R. M.; Seitz, S. P. *J. Med. Chem.* **1998**, *41*, 5113.
20. Han, W.; Pelletier, J. C.; Hodge, C. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3615.
21. Tossi, A.; Bonin, I.; Antcheva, N.; Norbedo, S.; Benedetti, F.; Miertus, S.; Nair, A. C.; Maliar, T.; Dal Bello, F.; Palù, G.; Romeo, D. *Eur. J. Biochem.* **2000**, *267*, 1715.
22. Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157.
23. Martyn, D. C.; Hoult, D. A.; Abell, A. D. *Aust. J. Chem.* **2001**, *54*, 391.
24. Le Nguyen, D.; Castro, B. *Pept. Chem.* **1987**, Protein Research Foundation: Osaka, 1988.