Oxazoline *N*-Oxide Mediated [3+2] Cycloadditions: Application to a Formal Synthesis of a (+)-β-Methylcarbapenem

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[3+2] Cycloaddition between a camphor-derived oxazoline *N*-oxide **9** and the γ,δ-unsaturated enamino ester **11** afforded the single adduct **6**. A stereoselective reduction of the enamino ester side chain allowed the control of the absolute configuration of the two additional asymmetric centres. Nitrogen protection and oxidative hydrolysis of the resulting product **13**, followed by further functional group manipulations, led to the β-lactam derivative **1**, a known precursor of the β-methylthienamycin derivative **2a**.

Introduction

Oxazoline *N*-oxide mediated cycloadditions have proved to be a valuable tool for the stereoselective synthesis of various natural or unnatural products.[1] We report here an extension of this methodology to a formal synthesis of a β-methylcarbapenem derivative **1** (Figure 1), synthetic precursor of carbapenem **2a**,[2] which is structurally related to thienamycin **2b**.[3] 1β-Methylcarbapenems display a broad-spectrum antibacterial activity, a good chemical stability and a resistance to renal dehydropeptidase DHP1. The major challenge in the synthesis of β-methylcarbapenem antibiotics is the stereocontrolled construction of four contiguous stereogenic centres. Two strategies have been used in previous syntheses of this family of antibiotics: either the four stereogenic centres are introduced diastereoselectively, or azetidinone **3**, in which three stereogenic centres are already set up, is used as starting material.[4]

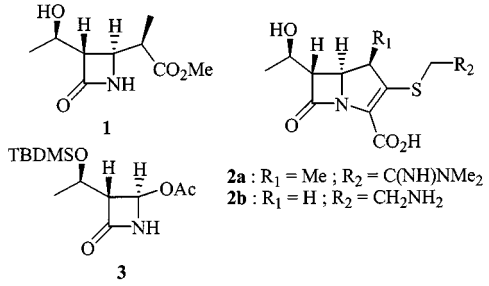
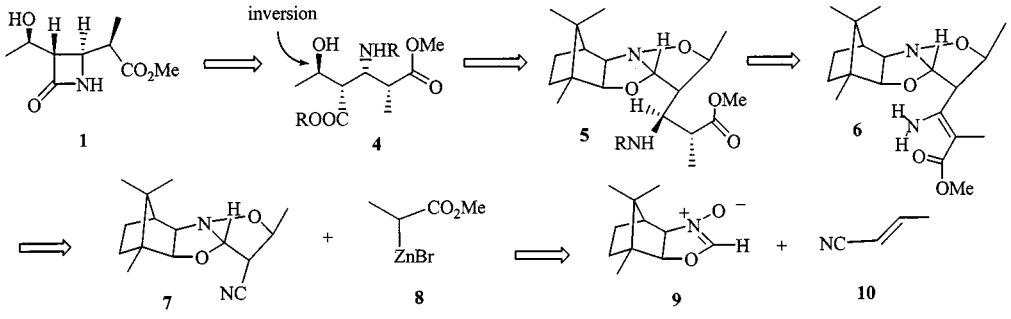


Figure 1. Thienamycin and β-methylthienamycin derivatives

In our retrosynthetic plan, compound **4**, a synthetic precursor of β-methylcarbapenem **1**, could be obtained after oxidative hydrolysis of compound **5**. The two additional stereogenic centres in **5** could be controlled by a diastereoselective reduction of the side chain in the camphor derivative **6** which is the result of a Blaise reaction between adduct **7** and the Reformatsky reagent **8**. According to previous studies,[1] adduct **7** could be obtained through a [3+2] cycloaddition between dipole **9** and 2-butenenitrile **10** (Scheme 1).

Results and Discussion

In relation with other studies directed towards the synthesis of the carbapenem antibiotic carpetimycin A, two routes were examined to prepare compound **6**. Thus, as in our initial planning, a cycloaddition reaction between dipole **9** and 2-butenenitrile **10** afforded smoothly the expected adduct **7** as the major product of the reaction.[5] In a more convergent synthesis, a cycloaddition between the γ,δ-unsaturated enamino ester **11**,[6] produced by a Blaise condensation[7] between the organozinc reagent **8** and nitrile **10**, was also examined. A surprising reactivity was observed in this case and adduct **6** was obtained after only two hours at 40 °C.[8] Longer reaction times induced the degradation of the adduct. Adduct **6** can be also prepared in a less convergent and less efficient route by Blaise con-



Scheme 1. β-Methylthienamycin synthetic precursor; retrosynthetic analysis

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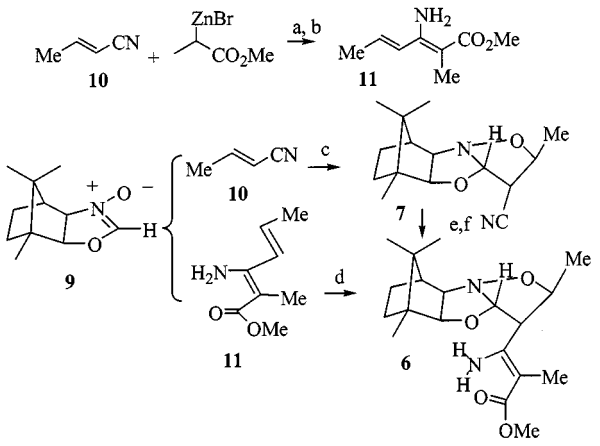
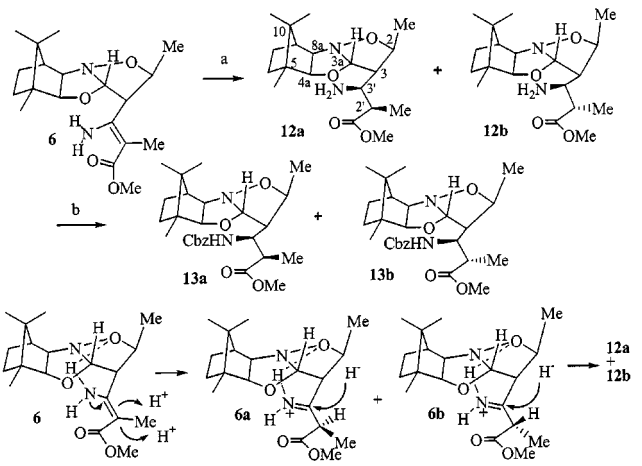


Scheme 2. Cycloadditions of oxazoline *N*-oxide with 2-butenenitrile and γ,δ-unsaturated enamino ester: (a) THF, reflux, 1 h; (b) aq. K_2CO_3, 60%; (c) CH_2Cl_2 $CaCO_3$, MS 4A, 40 °C, 16 h, 68%; (d) CH_2Cl_2, MS 4A, 40 °C, 2 h, 54%; (e) $BrCHMeCO_2Me$, Zn, THF, reflux, 45 min; (f) aq. K_2CO_3, 62%



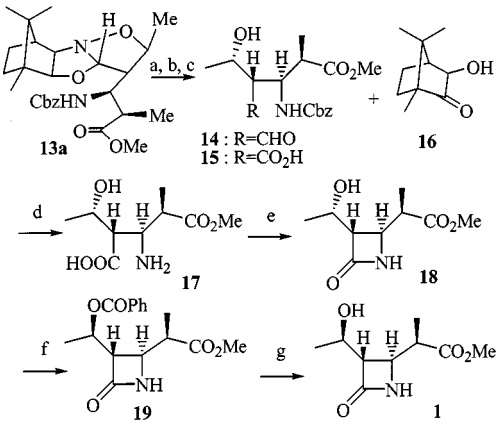
Scheme 3. Stereoselective reduction of enamino ester adduct: (a) $NaBH_3CN$, $MeOH/CH_2Cl_2$, 1:1, MeOH, 2 N, HCl; (b) CbzOSu, 5% aq.$NaHCO_3$, CH_2Cl_2, 20 °C, 1 h; **13a**: 67%, **13b**: 28%

densation between the nitrile derivative **7** and the Reformatsky reagent **8** (Scheme 2).

The corner stone step of the synthesis was the reduction of the enamino ester side chain in **6**. Sodium cyanoborohydride reduction[9] of the iminium intermediate **6**, when performed at low temperature, afforded stereoselectively a major product **12a**[10] along with a minor isomer, **12b** in a 70:30 ratio.[11] Purification of this mixture of isomers was achieved either by crystallisation in pentane or by chromatography after nitrogen protection as a carbobenzyloxy urethane. Thus, compounds **13a** and **13b** were isolated in 67% and 28% yield, respectively, from adduct **6**.

The modest diastereoselectivity (ca. 40%) observed during the protonation step giving rise to iminium intermediates **6a** or **6b**, could be the result of a noncontrolled conformational equilibrium of the side chain and also of a poor 1,3 asymmetric induction. In contrast, the hydride attack on the iminium intermediates **6a** or **6b**, in which a preferential conformation of the side chain due to hydrogen bonding between the iminium hydrogen and the two oxygens of the isoxazolidino-oxazolidino bicyclic framework is found, could explain the total diastereoselectivity observed in this step despite the configuration of the neighbouring carbon (Scheme 3).

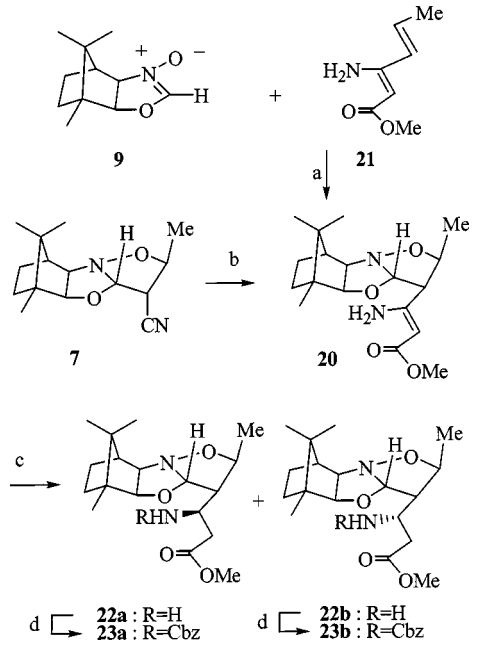
Oxidative hydrolysis, followed by oxidation[12] of the aldehyde intermediate **14** afforded the expected β-amino acid derivative **15** in 48% overall yield. Ketol **16**, which is a precursor of the chiral auxiliary, is recovered at this stage.[13] Reductive cleavage of the Cbz group proved to be difficult and an excess of palladium on charcoal was necessary. DCC lactamisation[14] of the resulting β-amino acid **17**[15] gave rise to the expected β-lactam derivative **18**. The coupling constants in the ^1H NMR spectrum of β-lactam **18** are in agreement with the literature data[16] and allowed the determination of the absolute configurations for the asymmetric centres.[14,17] Under Mitsunobu reaction conditions, the β-lactam **18** afforded the benzoyl derivative **19**. Final selective methanolysis gave rise to the known β-lactam **1**,[17,18] a precursor of the β-methylthienamycin derivative **2a** (Scheme 4). The same sequence of reactions performed from the minor compound **13b** afforded a β-lactam epimeric at the methyl side chain. The coupling constants in the ^1H NMR spectrum are in agreement with the literature data for this compound.[16,17]



Scheme 4. Oxidative hydrolysis and completion of the β-lactam synthesis: (a) (i) *m*CPBA, Et_2O, 20 °C, 30 min.(ii) $Na_2S_2O_4$, $NaHCO_3$, H_2O; (b) THF, 2 N HCl, 20 °C, 15 min; (c) $NaClO_2$, 10% aq. NaH_2PO_4/*t*BuOH, 1:4, 2-methyl-2-butene, 20 °C, 40 min, 48% from **13a**; (d) H_2, Pd–C, MeOH, 20 °C, 2 h; (e) DCC, MeCN, 60 °C, 3 h, 73% from **15**; (f) $PhCO_2H$, PPh_3, DIAD, THF, 2 h30, 20 °C, 77%; (g) MeONa, 10%, MeCN, 0 °C, 3 h. 0.2 N HCl, 67%

In order to clarify the role of the methyl group on the side chain during the reduction of the iminium intermediate, the same reaction was also studied on the desmethyl analogue, a formal precursor of thienamycin **2b** itself. Accordingly, adduct **7** was submitted to the Blaise reaction in the presence of the methyl bromoacetate Reformatsky reagent, to afford the enamino ester **20**. As previously, this compound was also prepared in a more convergent route by a cycloaddition reaction under mild reaction conditions between the oxazoline *N*-oxide **9** and the enamino ester **21**.[19] Low temperature sodium cyanoborohydride reduction of the camphor-derived enamino ester **20** afforded the

expected β-amino ester derivatives **22a** and **22b**. These compounds were directly protected as benzyl carbamates. At this stage, chromatographic purification allowed the isolation of the two isomeric carbamates **23a** and **23b** in 67% and 4% yields, respectively (*de* 89%) (Scheme 5). This result is in good agreement with the diastereoselectivity observed in the β-methylthienamycin series and confirms other observations concerning the diastereoselectivity of this reduction step.[20]



Scheme 5. Cycloaddition of oxazoline *N*-oxide with an unsubstituted γ,δ-unsaturated enamino ester and stereoselective reduction: (a) CH_2Cl_2, 40 °C, 2 h, 71%; (b) $BrCH_2CO_2Me$, Zn, THF, reflux, 45 min, K_2CO_3, H_2O, 60%; (c) $NaBH_3CN$, 1 M in THF, MeOH/2 N HCl, MeOH/CH_2Cl_2, 1:2, –90 °C, 15 h; (d) CbzOSu, $NaHCO_3$, H_2O, CH_2Cl_2, 20 °C, 1 h, **22a**, 67% from **20**, **23b**, 4% from **20**

Conclusion

In terms of efficiency, this synthesis is in the same range as Fukumoto′s synthesis[21] which uses an intramolecular asymmetric nitrone cycloaddition. Besides the preparation of a precursor of β-methylthienamycin, this synthesis also illustrates the possibility of chemio- and stereoselective transformations on adducts such as **6** in which an alcohol and a carbonyl group are inherently protected. An extension of this methodology to other natural products syntheses is in progress.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded at 250 MHz and 62.5 MHz, respectively. – Optical rotations were recorded at 20 °C. – Elemental analyses were performed at the CNRS, Gif sur Yvette, France. – Unless otherwise stated, chromatographic purifications were performed on columns with 230–400 mesh silica gel (Merck 9385) and the indicated solvent system. Dichloromethane, acetonitrile and trimethyl orthoacetate were distilled from calcium hydride. Toluene, diethyl ether and THF were distilled from sodium metal/benzophenone ketyl. Methanol was distilled from magnesium. Zinc powder was activated by successive washings with 2 N hydrochloric acid, water, ethanol and acetone, and was stored under argon in a Schlenk. *trans*-Crotonitrile **(10)** was prepared isomerically pure from crotonic acid by the method described by Lohaus.[22] Chloroform used for optical measurements was filtered through basic alumina before use. All nonaqueous reactions were performed under an argon atmosphere using oven-dried glassware.

Methyl (2*Z*,4*E*)-3-Amino-2-methyl-2,4-hexadienoate (11): The following procedure is typical for Blaise reactions with nitriles. A suspension of activated zinc powder (3.27 g, 50 mmol) in tetrahydrofuran (30 mL) was heated at reflux and a few drops of methyl 2-bromopropionate were added. When the reaction mixture turned green, *trans*-crotonitrile **10** (670 mg, 10 mmol) was added in one portion, stirring was set in motion, and methyl 2-bromopropionate (2.3 mL, 2 mmol) was added dropwise over 45 min. After completion of the addition, the mixture was cooled to room temperature, diluted with tetrahydrofuran (90 mL) and an aqueous 50% potassium carbonate solution (13 mL) was added. The mixture was vigorously stirred for 30 min, then filtered through a pad of celite, which was then rinsed with tetrahydrofuran. The filtrate was concentrated in vacuo and the oily residue taken up with dichloromethane (100 mL), washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by chromatography on florisil (100–200 mesh, 50% ether/pentane, R_f = 0.8) to give the title compound as a yellow oil (930 mg, 63%). A lower yield was obtained when purification was performed on silica gel. – IR (film): $\tilde{\nu}$ = 3400, 1730, 1650 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 6.35 (d, *J* = 16.2 Hz, 1 H, C4-H), 6.20 (m, 3 H, C5-H and NH_2), 3.65 (s, 3 H, OMe), 1.85 (dd, *J* = 6.3 Hz, 1 Hz, 3 H, C6-H), 1.80 (s, 3 H, CH_3–C2). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.5 (CO), 153.1 (C3), 130.7 (C4), 127.1 (C5), 90.9 (C2), 50.7 (OMe), 18.5 (CH_3–C2), 12.1 (C6). – MS (CI, NH_3); *m*/*z*: 156 [MH^+].

Methyl (2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*,2′*Z*)-3-(2,5,10,10-Tetramethyloctahydro-2*H*-5,8-methano-isoxazolo[3,2-*b*]benzoxazol-3-yl)-3′-amino-2′-methyl-2′-propenoate (6). – Cycloaddition Between Oxazoline *N*-Oxide (9) and Enamino Ester 11: This procedure is typical for cycloadditions between oxazoline *N*-oxide **(9)** and conjugated enamino esters. To a suspension of (+)-3-hydroxyaminoisoborneol hydrochloride (4 g, 18 mmol) in dichloromethane was added trimethyl orthoformate (7.9 mL, 72 mmol, 4 equiv.). The white suspension was stirred at 40 °C for 3.5 h. Powdered 4-Å molecular sieves (2 g) were then added and the mixture stirred for an additional 30 min. The enamino ester **11** (8.4 g, 54 mmol, 3 equiv.) was then added and the reaction mixture stirred for 2 h at reflux. After cooling to room temperature, the solution was filtered through a pad of celite, which was then rinsed with dichloromethane. The filtrate was concentrated in vacuo and the residue purified by chromatography (50% ether/pentane, R_f = 0.5) to give the cycloadduct **6** as a white solid (3.4 g, 54%). – IR (film moistened with $CHCl_3$): $\tilde{\nu}$ = 3400, 1730 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 6.70, (s, 2 H, NH_2), 5.43 (d, *J* = 5.6 Hz, 1 H, C3a-H), 4.10 (dq, *J* = 10.8 Hz, *J* = 5.7 Hz, 1 H, C2-H), 3.91 (d, *J* = 7.6 Hz, 1 H, C4a-H), 3.70 (s, 3 H, OMe), 3.55 (d, *J* = 7.6 Hz, 1 H, C8a-H), 3.05 (dd, *J* = 10.8, *J* = 5.6 Hz, 1 H, C3-H), 2.12 (d, *J* = 4 Hz, 1 H, C8-H), 1.80 (s, 3 H, Me–C2′), 1.70 (m, 2 H, C7-H × 2), 1.40 (m, 1 H, one of C6-H), 1.25 (d, *J* = 6 Hz, 3 H, Me–C2), 1.15 (m, 1 H, one of C6-H), 0.95, 0.90, 0.80 (3s, 9 H, CH_3 × 3). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.2 (CO), 153.9 (C3′), 99.3 (C3a), 92.4 (C2′), 90.7 (C4a), 78.4 (C2), 75.3 (C8a), 55.0 (C3), 50.7 (OMe), 49.6 (C8), 49.1

(C5), 45.0 (C10), 31.6 (C6), 25.8 (C7), 15.8 (Me–C2′), 12.4 (Me–C2), 22.3, 18.6, 10.9 ($CH_3 \times 3$). – MS (CI, NH_3); *m*/*z*: 351 [MH^+], 180, 172, 156. – $[\alpha]_D^{20}$ = –161 (*c* = 1, $CHCl_3$). – $C_{19}H_{30}N_2O_4$ (350.46195): calcd. C 65.12, H 8.63, N 7.99; found C 64.72, H 8.62, N 7.59.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-(2,5,10,10-Tetramethyl-octahydro-2*H*-5,8-methano-isoxazolo[3,2-*b*]benzoxazol-3-carbonitrile (7). – Cycloaddition Between Oxazoline *N*-Oxide (9) and Crotonitrile (10): To a suspension of 3-hydroxylaminoisoborneol hydrochloride (8 g, 36.mmol) and calcium carbonate (3.6 g, 36 mmol, 1 equiv.) in dichloromethane (150 mL) was added trimethyl orthoformate (15.8 mL, 145 mmol, 4 equiv.). The white suspension was stirred for 4 h at reflux, then *trans*-crotonitrile **10** (20.8 g, 300 mmol, 8 equiv.), was added. The mixture was stirred overnight at reflux, then cooled to room temperature and filtered through a pad of celite, eluting with dichloromethane. The filtrate was concentrated in vacuo and the residue purified by chromatography (15% ethyl acetate/heptane) to give, in order of elution, a small amount of the *exo* cycloadduct (10%), followed by the *endo* cycloadduct **7** (6.6 g, 70%), which was isolated as a white powder. – IR (film moistened with $CHCl_3$): $\tilde{\nu}$ = 2950, 2260 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 5.43 (d, *J* = 6.7 Hz, 1 H, C3a-H), 4.28 (dq, *J* = 10.1, 5.9 Hz, 1 H, C2-H), 4.12 (d, *J* = 7.5 Hz, 1 H, C4a-H), 3.31 (d, *J* = 7.5 Hz, 1 H, C8a-H), 2.92 (dd, *J* = 10.1, 6.7 Hz, 1 H, C3-H), 2.12 (d, *J* = 4 Hz, 1 H, C8-H), 1.70 (m, 2 H, C7-H × 2), 1.42 (d, *J* = 6 Hz, 3 H, Me–C2), 1.40 (m, 2 H, C6-H × 2), 0.96, 0.88, 0.78 (3s, 9 H, $CH_3 \times 3$). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 115.2 (CN), 97.0 (C3a), 90.2 (C4a), 75.6 (C2), 75.1 (C8a), 48.9 (C3), 48.6 (C5), 45.8 (C10), 45.5 (C8), 31.3 (C6), 25.5 (C7), 16.5 (Me–C2), 22.1, 18.7, 10.6 ($CH_3 \times 3$). – MS (CI, NH_3); *m*/*z*: 263 [MH^+], 180. – $[\alpha]_D^{20}$ = –167 (*c* = 1, $CHCl_3$). – $C_{15}H_{22}N_2O_2$ (262.35497): calcd. C 68.67, H 8.45, N 10.68; found C 68.22, H 7.99, N 10.25.

Preparation of Compound 6 by Blaise Reaction of Cycloadduct 7: This reaction was carried out according to the typical procedure for Blaise reactions described for the preparation of **11**, starting from cycloadduct **7** (260 mg, 1 mmol), zinc powder (327 mg, 5 mmol), and methyl 2-bromopropionate (450 μL, 4 mmol). Purification of the crude product by chromatography (40% pentane/ether, R_f = 0.55) gave compound **6** as a white solid (217 mg, 62%), identical in all respect to the one prepared by cycloaddition with enamino ester **11**.

Methyl (2*S*,2′*RS*,3*S*,3′*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-(2,5,10,10-Tetramethyl-octahydro-2*H*-5,8-methano-isoxazolo[3,2-*b*]benzoxazol-3-yl)-3′-amino-2′-methylpropanoate (12): A solution of the enamino ester **6** (3.33 g, 9.5 mmol) in 2:1 dichloromethane/methanol (93 mL) containing a few crystals of bromocresol green was cooled to –90 °C with stirring and a few drops of a 2 N solution of hydrogen chloride in methanol (prepared by careful addition of acetyl chloride to anhydrous methanol at 0 °C) were added until the solution colour turned from blue to yellow. Sodium cyanoborohydride (779 mg, 12.5 mmol, 1.3 equiv.) was then added in one portion, resulting in a blue colour. A 2 N hydrogen chloride solution in methanol (30 mL) was then added dropwise over 15 h (syringe pump), in order to maintain a persistent yellow colour. After completion of the addition, the solution was slowly warmed to –20 °C, and a 0.1 N sodium hydroxide solution was added until the solution turned deep blue. Brine (50 mL) was added and the mixture was extracted with dichloromethane (2 × 100 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a mixture of isomeric β-amino esters **12a** and **12b** (3.3 g; 99%), which were not separated at this stage but immediately carried forward to the next reaction.

Methyl (2*S*,2′*R*,3*S*,3′*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-(2,5,10,10-Tetramethyl-octahydro-2*H*-5,8-methano-isoxazolo[3,2-*b*]benzoxazol-3-yl)-3′-(phenylmethyloxycarbonyl)amino-2′-methylpropanoate (13a): (Benzyloxycarbonyloxy)succinimide (CbzOSu, 2.8 g, 11.25 mmol, 1.2 equiv.) was added to a solution of amines **12a** and **12b** (3.3 g, 9.4 mmol) in a mixture of dichloromethane (100 mL) and aqueous 5% sodium hydrogen carbonate solution (100 mL). The biphasic mixture was vigorously stirred for 1 h and the layers separated. The aqueous layer was extracted with dichloromethane (100 mL) and the combined organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude product by chromatography (30% ethyl acetate/pentane) gave, in order of elution, the major isomer **13a** (R_f = 0.65, 3.07 g, 67%), followed by the minor isomer **13b** (R_f = 0.4, 1.28 g, 28%). – **13a:** IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1740, 1680 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.40 (broad s, 5 H, Ar-H), 5.35 (d, *J* = 5.6 Hz, 1 H, C3a-H), 5.30 (d, *J* = 7.5 Hz, 1 H, NH), 5.15 (m, 2 H, Ar–CH_2), 4.15 (dq, *J* = 10.6 Hz, *J* = 6.4 Hz, 1 H, C2-H), 3.70 (s, 3 H, OMe), 3.69 (obscured m, 2 H, C4a-H and C3′-H), 3.35 (d, *J* = 7.5 Hz, 1 H, C8a-H), 2.80 (m, 1 H, C2′-H), 2.10 (d, *J* = 4.2 Hz, 1 H, C8-H), 1.80 (m, 1 H, C3-H), 1.70 (m, 2 H, C7-H × 2), 1.40 (m, 2 H, C6-H), 1.20 (2d, *J* = 6.4 Hz, 6 H, Me–C2 and Me–C2′), 0.95, 0.85 and 0.80 (3s, 9 H, $CH_3 \times 3$). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.1 (CO_2), 155.7 ($NHCO_2$), 136.2, 127.9, 127.5 (Ar), 99.2 (C3a), 89.5 (C4a), 77.9 (C2), 72.8 (C8a), 66.1 (CH_2-Ar), 54.6 (C3′), 51.4 (OMe), 50.5 (C3), 49.0 (C8), 48.3 (C5), 44.7 (C10), 43.1 (C2′), 31.1 (C6), 25.1 (C7), 15.4 (Me–C2), 14.4 (Me–C2′), 21.7. 18.2 and 10.4 ($CH_3 \times 3$). – MS (CI, NH_3); *m*/*z*: 487 [MH^+], 308, 180. – $[\alpha]_D^{20}$ = –57.3 (*c* = 1, $CHCl_3$). – HRMS calculated for $C_{27}H_{38}N_2O_6$: 487.28081; found 487.28086. – **13b:** IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1740, 1680 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.40 (broad s, 5 H, Ar-H), 5.40 (d, *J* = 10.4 Hz, 1 H, NH), 5.30 (d, *J* = 6.1 Hz, 1 H, C3a-H), 5.10 (m, 2 H, Ar–CH_2), 4.15 (dq, *J* = 10.6 Hz, *J* = 6.4 Hz, 1 H, C2-H), 3.70 (obscured m, 2 H, C4a-H and C3′-H), 3.65 (s, 3 H, OMe), 3.30 (d, *J* = 7.5 Hz, 1 H, C8a-H), 2.80 (m, 1 H, C2′-H), 2.10 (d, *J* = 4.2 Hz, 1 H, C8-H), 1.90 (m, 1 H, C3-H), 1.70 (m, 2 H, C7-H × 2), 1.40 (m, 2 H, C6-H), 1.30 (d, *J* = 5.8 Hz, 3 H, Me–C2′), 1.25 (d, *J* = 7 Hz, 3 H, Me–C2), 0.95, 0.85 and 0.80 (3s, 9 H, $CH_3 \times 3$). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.5 (CO_2), 155.9 ($NHCO_2$), 136.7, 128.4, 128.0 (Ar), 99.4 (C3a), 90.1 (C4a), 78.0 (C2), 73.5 (C8a), 66.5 (CH_2-Ar), 54.9 (C3′), 51.8 (OMe), 51.0 (C3), 49.4 (C8), 48.7 (C5), 45.3 (C10), 43.6 (C2′), 31.5 (C6), 25.5 (C7), 16.1 (Me–C2), 15.2 (Me–C2′), 22.1, 18.6 and 10.9 ($CH_3 \times 3$). – MS (CI, NH_3); *m*/*z*: 487 [MH^+], 308, 180. – $[\alpha]_D^{25}$ = –56.3 (*c* = 1, $CHCl_3$). – HRMS calculated for $C_{27}H_{38}N_2O_6$: 487.28081; found 487.28081.

Methyl (2*R*,3*S*,4*S*,5*S*) 4-Formyl-5-hydroxy-2-methyl-3-(phenylmethoxycarbonyl)aminohexanoate (14): *m*-Chloroperoxybenzoic acid (1.22 g, 7.1 mmol, 5 equiv.) was added in one portion to a solution of amine **13a** (691 mg, 1.42 mmol) in diethyl ether (35 mL). The clear solution was stirred for 30 min at room temperature and the unchanged peracid was quenched by addition of an aqueous 10% sodium hydrogen carbonate/10% sodium thiosulfate (35 mL). The biphasic solution was vigorously stirred at room temperature for 30 min, then the layers were separated. The organic layer was washed with water, brine (25 mL each), dried (Na_2SO_4), filtered and concentrated in vacuo to give a white foam which was immediately redissolved in tetrahydrofuran (35 mL). A 2 N hydrochloric acid solution (35 mL) was added and the mixture was stirred at room temperature for 15 min, then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed successively with 5% sodium hydrogen carbonate solution, pH 7 buffer solution and brine (50 mL each), dried (Na_2SO_4) and then

filtered and concentrated in vacuo. Purification of the crude product by chromatography (50% ethyl acetate/pentane) gave, in order of elution, the recovered ketol **16** (R_f = 0.65, 210 mg, 88% recovery), followed by the aldehyde **14** (R_f = 0.4, 335 mg, 70% for two steps) as an amorphous white solid. – IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1740, 1720 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 9.90 (broad s, 1 H, CHO), 7.30 (broad s, 5 H, Ar-H), 5.60 (d, *J* = 10.3 Hz, 1 H, NH), 5.10 (m, 2 H, Ar–CH_2), 4.20 (m, 2 H, C3-H and C5-H), 3.70 (s, 3 H, OMe), 2.80 (m, 1 H, C4-H), 2.60 (m, 1 H, C2-H), 1.40 (d, *J* = 6.3 Hz, 3 H, C6-H × 3), 1.20 (d, *J* = 7.1 Hz, 3 H, Me–C2). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 205.7 (CHO), 174.8 (*C*O_2Me), 156.4 ($NHCO_2$), 136.1, 128.4, 128.0, 127.8 (Ar), 67.5 (C5), 66.8 (Ar–CH_2), 58.9 (C3), 52.0 (C4), 51.9 (OMe), 42.9 (C2), 22.2 (C6), 13.8 (Me–C2). – MS (CI, NH_3); *m*/*z*: 338 [MH^+], 320, 294, 160. – $[\alpha]_D^{20}$ = +46 (*c* = 0.83, $CHCl_3$). – $C_{17}H_{23}NO_6$ (337.37596): calcd. C 60.52, H 6.87, N 4.15; found C 60.41, H 6.91, N 4.10.

Methyl (2*R*,3*S*,4*S*,5*S*)-4-Carboxy-5-hydroxy-2-methyl-3-(phenylmethoxycarbonyl)aminohexanoate (15): To a solution of the aldehyde **14** (200 mg, 0.6 mmol) and 2-methyl-2-butene (7.5 mL) in *tert*-butyl alcohol (20 mL) was added an aqueous 10% sodium chlorite/10% sodium dihydrogen phosphate solution (7 mL). The colourless solution was stirred at room temperature for 30 min. Water (40 mL) was added and the mixture was extracted with ethyl acetate (5 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by preparative thin-layer chromatography (10% methanol/dichloromethane). The baseline was collected to give the acid **15** as a white solid (145 mg, 69%). – IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3400, 1760, 1740 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.30 (broad s, 5 H, Ar-H), 5.90 (d, *J* = 10.3 Hz, 1 H, NH), 5.10 (m, 2 H, Ar–CH_2), 4.20 (m, 1 H, C5-H), 4.10 (m, 1 H, C3-H), 3.65 (s, 3 H, OMe), 2.65 (m, 1 H, C4-H), 2.50 (m, 1 H, C2-H), 1.40 (d, *J* = 6.2 Hz, 3 H, C6-H × 3), 1.20 (d, *J* = 7 Hz, 3 H, Me–C2). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 178.0 (CO_2H), 175.1 (*C*O_2Me), 156.6 ($NHCO_2$), 136.3, 128.4, 128.1, 127.9 (Ar), 67.6 (C5), 66.9 (Ar–CH_2), 55.1 (C3), 52.0 (C4), 51.7 (OMe), 43.7 (C2), 21.4 (C6), 14.1 (Me–C2). – MS (CI, NH_3); *m*/*z*: 354 [MH^+], 310. – $[\alpha]_D^{20}$ = –1.5 (*c* = 0.74, $CHCl_3$). – HRMS calculated for $C_{17}H_{23}NO_7$: 376.13722; found 376.13697.

Methyl (2*R*,3*S*,4*S*,5*S*)-3-Amino-4-carboxy-5-hydroxy-2-methylhexanoate (17): To a solution of the acid **15** (145 mg, 041 mmol) in anhydrous methanol (13 mL) was added 10% palladium on carbon (145 mg) and the mixture was stirred under an atmosphere of hydrogen for 2.5 h. The black suspension was then filtered through a pad of celite, eluting with methanol. The filtrate was concentrated in vacuo to give the unprotected amino acid **17** as a white foam (90 mg, 99%) which was used in the next reaction without further purification. – IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3400, 1760, 1740 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 4.00 (m, 1 H, C5-H), 4.10 (m, 1 H, C3-H), 3.70 (s, 3 H, OMe), 2.90 (m, 1 H, C4-H), 2.30 (m, 1 H, C2-H), 1.40 (d, 6 H, 3 × C-H and Me–C2). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 177.4 (CO_2H), 175.2 (*C*O_2Me), 68.1 (C5), 53.2 (C3), 52.1 (OMe), 50.0 (C4), 41.7 (C2), 22.2 (C6), 12.8 (Me–C2). – MS (CI, NH_3); *m*/*z*: 220 [MH^+], 144.

(3*S*,4*S*)-3-[(1*S*)-Hydroxyethyl]-4-[(1*R*)-methoxycarbonyl]ethyl-2-azetidinone (18): A solution of the amino acid **17** (90 mg, 0.41 mmol) and dicyclohexylcarbodiimide (170 mg, 0.82 mmol, 2 equiv.) in acetonitrile (5 mL) was stirred at reflux for 1.5 h. After cooling to room temperature, the solution was diluted with ethyl acetate (5 mL) and the solids were removed by filtration. The filtrate was concentrated in vacuo and the residue purified by preparative thin-layer chromatography (10% methanol/dichloromethane, R_f = 0.4) to give the β-lactam **18** as a colourless oil (61 mg, 73%). – IR (film): $\tilde{\nu}$ = 3400, 1740, 1735 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 6.30 (s, 1 H, NH), 4.11 (m, 1 H, C*H*–OH), 3.71 (s, 3 H, OMe), 3.69 (d, *J* = 2.2 Hz, 1 H, C4-H), 3.06 (dd, *J* = 6.3 Hz, *J* = 2.2 Hz, 1 H, C3-H), 2.67 (m, 1 H, C*H*–CO_2Me), 1.35 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$–CHOH), 1.28 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$–CH–CO_2Me). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.3 (*C*O_2Me), 168.6 (C2), 65.8 (CHOH), 61.4 (C4), 52.6 (C3), 52.1 (OMe), 43.0 (*C*HCO_2Me), 21.0 (*C*H$_3$–CHOH), 13.4 (*C*H$_3$–CHCO_2Me). – MS (CI, NH_3); *m*/*z*: 219 [MNH_4^+], 202 [MH^+], 141. – $[\alpha]_D^{20}$ = –12.5 (*c* = 1, $CHCl_3$). – $C_9H_{15}NO_4$ (201.2242): calcd. C 53.72, H 7.51, N 6.96; found C 53.69, H 7.63, N 6.51.

(3*S*,4*S*)-3-[(1*R*)-Benzoyloxyethyl]-4-[(1*R*)-methoxycarbonyl]ethyl-2-azetidinone (19): Benzoic acid (146 mg, 1.2 mmol, 4 equiv.) was added to a cooled (0 °C) solution of azetidinone **18** (60 mg, 0.3 mmol) and triphenylphosphine (274 mg, 1.05 mmol, 3.5 equiv.) in tetrahydrofuran (2 mL). The solution was stirred for 5 min at 0 °C and diisopropylazodicarboxylate (DIAD, 235 μL, 1.2 mmol, 4 equiv.) was added. The cooling bath was removed and the solution stirred at room temperature for 2.5 h. The solvent was evaporated and the residue purified by chromatography (50% ethyl acetate/pentane, R_f = 0.35) to give the ester **19** as a colourless oil (70 mg, 77%). – IR (film): $\tilde{\nu}$ = 3300, 1770, 1735, 1720 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.02 (m, 2 H, Ar-H), 7.57 (m, 1 H, Ar-H), 7.44 (m, 2 H, Ar-H), 6.16 (s, 1 H, NH), 5.50 (dq, *J* = 7.3 Hz, *J* = 6.4 Hz, 1 H, C*H*–OCOPh), 3.90 (dd, *J* = 6.1 Hz, *J* = 2.3 Hz, 1 H, C4-H), 3.70 (s, 3 H, OMe), 3.33 (dd, *J* = 7.3 Hz, *J* = 2.3 Hz, 1 H, C3-H), 2.73 (dq, *J* = 7.1 Hz, *J* = 6.1 Hz, 1 H, C*H*CO_2Me), 1.48 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$–CHOCOPh), 1.24 (d, 3 H, C*H*$_3$–CHCO_2Me). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.4 (*C*O_2Me), 166.7 (C2), 165.5 (Ph*C*O_2), 133.1, 130.0, 129.6, 128.3 (Ar), 68.6 (*C*HOCOPh), 59.2 (C4), 53.7 (C3), 51.9 (OMe), 42.7 (*C*HCO_2Me), 18.4 (*C*H$_3$CHOCOPh), 13.0 (*C*H$_3$CHCO_2Me). – MS (CI, NH_3); *m*/*z*: 306 [MH^+]. – $[\alpha]_D^{20}$ = –26.4 (*c* = 0.53, $CHCl_3$). – HRMS calculated for $C_{16}H_{19}NO_5$: 328.1160; found 328.1163.

(3*S*,4*S*)-3-[(1*R*)-Hydroxyethyl]-4-[(1*R*)-methoxycarbonyl]ethyl-2-azetidinone (1): A solution of the ester **19** (26 mg, 0.085 mmol) in acetonitrile (1 mL) was cooled to 0 °C and a 10% solution of sodium methoxide in methanol (29 μL) was added. The solution was stirred at 0 °C for 3 h, ethyl acetate (5 mL) was added and the mixture was neutralised by addition of a few drops of 0.2 N hydrochloric acid. The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (10% methanol/ethyl acetate, R_f = 0.64) to give the azetidinone **1** as a white solid (11.5 mg, 67%), m.p. 102 °C. – IR (film): $\tilde{\nu}$ = 3400, 1770, 1735 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 6.15 (s, 1 H, NH), 4.16 (m, 1 H, C*H*–OH), 3.77 (d, *J* = 7.8 Hz, *J* = 2.1 Hz, 1 H, C4-H), 3.72 (s, 3 H, OMe), 2.98 (dd, *J* = 7.0 Hz, *J* = 2.1 Hz, 1 H, C3-H), 2.67 (m, 2 H, C*H*–CO_2Me and OH), 1.31 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$–CHOH), 1.27 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$–CH–CO_2Me). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.8 (*C*O_2Me), 167.7 (C2), 65.8 (CHOH), 62.6 (C4), 53.6 (C3), 52.2 (OMe), 43.20 (*C*HCO_2Me), 21.1 (*C*H$_3$–CHOH), 13.7 (*C*H$_3$–CHCO_2Me). – MS (CI, NH_3); *m*/*z*: 219 [MNH_4^+], 202 [MH^+]. – $[\alpha]_D^{20}$ = –44.8 (*c* = 0.22, $CHCl_3$). – HRMS (electrospray) calculated for $C_9H_{15}NNaO_4$ (M + Na): 224.0898; found 224.0896.

Methyl (2*Z*,4*E*)-3-Amino-2,4-hexadienoate (21): This reaction was carried out according to the typical procedure for Blaise reactions described for the preparation of **11**, starting from crotonitrile **10** (2 g, 30 mmol), zinc powder (9.7 g, 150 mmol) and methyl bromacetate (11.3 mL, 120 mmol). Purification of the crude product by

chromatography (50% ether/pentane, R_f = 0.7) gave the enamino ester **21** as a white solid (2.8 g, 67%). – IR (film moistened with $CHCl_3$): $\tilde{\nu}$ = 3400, 1730, 1650 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 6.25 (dq, *J* = 16 Hz, *J* = 6.7 Hz, 1 H, C5-H), 6.20 (dd, *J* = 16 Hz, *J* = 1.1 Hz, 3 H, C4-H), 4.65 (s, 1 H, C2-H), 3.65 (s, 3 H, OMe), 1.85 (dd, *J* = 6.7 Hz, *J* = 1.1 Hz, 3 H, C6-H × 3). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.8 (*C*O_2Me), 156.1 (C3), 130.6 (C4), 128.3 (C3), 85.5 (C2), 50.3 (OMe), 18.2 (C6). – MS (CI, NH_3); *m*/*z*: 142 [MH^+]. – HRMS (electrospray) calculated for $C_7H_{11}NNaO_2$ (M + Na): 164.0687; found 164.0687.

Methyl (2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*,2′*Z*)-3-(2,5,10,10-Tetramethyl-octahydro-2*H*-5,8-methano-isoxazolo[3,2-*b*]benzoxazol-3-yl)-3′-amino-2′-propenoate (20): This compound was prepared by cycloaddition between oxazoline *N*-oxide **(9)** and enamino ester **21**, following the typical procedure described for the preparation of cycloadduct **11**, starting from (+)-3-hydroxyaminoisoborneol hydrochloride (1.1 g, 5 mmol), trimethyl orthoformate (2.16 mL, 20 mmol, 4 equiv.) and enamino ester **21** (2.8 g, 20 mmol, 4 equiv.) in the presence of 4Å molecular sieves (500 mg). Purification by chromatography (50% ether/pentane, R_f = 0.3) gave the title compound as a white solid (1.18 g, 71%). – IR (film moistened with $CHCl_3$): $\tilde{\nu}$ = 3400, 1730 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 5.43 (d, *J* = 7.5 Hz, 1 H, C3a-H), 4.55 (s, 1 H, C2′-H), 4.05 (dq, *J* = 10.7 Hz, *J* = 5.6 Hz, 1 H, C2-H), 3.91 (d, *J* = 7.5 Hz, 1 H, C4a-H), 3.66 (s, 3 H, OMe), 3.48 (d, *J* = 7.5 Hz, 1 H, C8a-H), 2.40 (dd, *J* = 10.7 Hz, *J* = 5.7 Hz, 1 H, C3-H), 2.12 (d, *J* = 3.8 Hz, 1 H, C8-H), 1.70 (m, 2 H, C7-H), 1.40 (m, 2 H, C6-H), 1.25 (d, *J* = 5.6 Hz, 2 H, Me–C2), 0.95, 0.90, 0.80 (3s, 9 H, CH_3 × 3). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.3 (*C*O_2Me), 157.7 (C3′), 99.7 (C3a), 90.7 (C4a), 86.1 (C2′), 78.2 (C2), 74.8 (C8a), 59.6 (C3), 50.4 (OMe), 49.6 (C8), 49.1 (C5), 45.4 (C10), 31.7 (C6), 25.8 (C7), 16.3 (Me–C2), 22.4, 18.7, 10.3 (CH_3 × 3). – MS (CI, NH_3); *m*/*z*: 337 [MH^+], 181. – $[\alpha]_D^{20}$ = –199 (*c* = 0.94, $CHCl_3$). – HRMS (electrospray) calculated for $C_{18}H_{28}N_2NaO_4$ (M + Na): 359.1946; found 359.1956.

Methyl (2*S*,3*S*,3′*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-(2,5,10,10-Tetramethyl-octahydro-2*H*-5,8-methano-isoxazolo[3,2-*b*]benzoxazol-3-yl)-3′-aminopropanoate (22): A blue solution of the enamino ester **20** (700 mg, 2.08 mmol) in 2:1 dichloromethane/methanol (20 mL) containing few crystals of bromocresol green was cooled to –90 °C with stirring, and few drops of a 2 N methanolic hydrogen chloride solution were added, resulting in a change of colour from blue to yellow. A 1 M sodium cyanoborohydride solution in tetrahydrofuran (3.12 mL, 31.2 mmol, 1.5 equiv.) was added dropwise. When the solution colour turned to blue, a 2 N methanolic hydrogen chloride solution (6.6 mL) was added dropwise over 15 h (syringe pump). After completion of the addition, the yellow solution was progressively warmed to –20 °C and was neutralised by addition of an aqueous 0.1 N sodium hydroxide solution until the colour turned persistent blue. Brine (30 mL) was added, and the mixture extracted by dichloromethane (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to give a mixture of isomeric β-amino esters **22a** and **22b** (700 mg, 99%), which was used in the next reaction without further purification.

Methyl (2*S*,3*S*,3′*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-(2,5,10,10-Tetramethyl-5,8-methano-octahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3)-3′-yl-3′-(phenylmethyloxycarbonyl)aminopropanoate (23a): (Benzyloxycarbonyloxy)succinimide (618 mg, 2.5 mmol, 1.2 equiv.) was added to a solution of amines **22a** and **22b** (700 mg, 2.07 mmol) in a mixture of dichloromethane (20 mL) and aqueous 5% sodium hydrogen carbonate solution (20 mL). The biphasic mixture was vigorously stirred for 1 h, and the layers were separated. The aqueous layer was extracted with dichloromethane (50 mL) and the combined organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude product by chromatography (35% ethyl acetate/pentane) gave, in order of elution, the major isomer **23a** (R_f = 0.5, 659 mg, 67%), followed by the minor isomer **23b** (R_f = 0.4, 37 mg, 4%). – **23a:** IR (film moistened with $CHCl_3$): $\tilde{\nu}$ = 3400, 1740 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.25 (broad s, 5 H, Ar-H), 5.25 (m, 2 H, C3-H and NH), 5.05 (m, 2 H, Ar–CH_2), 4.35 (m, 1 H, C2-H), 3.65 (d, *J* = 7.4 Hz, 1 H, C4-H), 3.60 (s, 3 H, OMe), 3.35 (d, *J* = 7.4 Hz, 1 H, C8a-H), 2.60 (m, 2 H, C2′-H × 2), 2.00 (d, *J* = 3.8 Hz, 1 H, C8-H), 1.85 (m, 1 H, C3-H), 1.60 (m, 2 H, C7-H × 2), 1.40 (m, 2 H, C6-H × 2), 1.20 (d, *J* = 5.6 Hz, 3 H, Me–C2), 0.85, 0.80, 0.70 (3s, 9 H, CH_3 × 3). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.3 (*C*O_2Me), 155.4 (NH*C*O_2), 136.4, 128.2, 127.8 (Ar), 99.5 (C3a), 89.8 (C4a), 78.0 (C2), 72.9 (C8a), 66.3 (Ar–CH_2), 56.3 (C3′), 51.6 (OMe), 49.2 (C3), 48.5 (C5), 45.3 (C8), 45.0 (C10), 38.6 (C2′), 31.3 (C6), 25.3 (C7), 15.8 (Me–C2), 21.9, 18.4, 10.6 (CH_3 × 3). – MS (CI, NH_3); *m*/*z*: 473 [MH^+]. – $[\alpha]_D^{20}$ = –53 (*c* = 2.1, $CHCl_3$). – HRMS (electrospray) calculated for $C_{26}H_{36}N_2NaO_4$ (M + Na): 495.24710; found 495.24711.

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[19] Enamino ester **21** was prepared in 67% yield by treatment of (*E*)-2-butenenitrile with ethyl bromoacetate (4 equiv.) and zinc (5 equiv.) in refluxing THF, followed by work up with an aqueous solution of K_2CO_3.

[20] With a cycloadduct substituted by a *gem* dimethyl group at C2, the diastereomer corresponding to compound **22b** is the only product of the reaction. This result is also in agreement with a conformational restriction of the side chain due to hydrogen bonding in the iminium intermediate and a diastereoselective attack of hydride at the *Re* face of this iminium (unpublished work).

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