Oxazoline *N*-Oxide Mediated [2+3] Cycloadditions. Application to a formal Synthesis of (+)-Carpetimycin A.

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SUPPORTING INFORMATION

Experimental Section

Generalities. ^{1}H 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 a column with 230-400 mesh silica gel (Merck 9385) using 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 2N hydrochloric acid, water, ethanol and acetone, and was stored under argon in a Schlenk flask. Chloroform used for optical measurements was filtered through basic alumina before use. All non-aqueous reactions were performed under an argon atmosphere using oven-dried glassware.

(2*Z*)-3-Amino-5-methyl-2,4-hexadienoic acid methyl ester (9).

A suspension of activated zinc powder (20 g, 0.3 mol) in dry tetrahydrofuran (185 mL) was stirred at reflux while a few drops of methyl bromoacetate were added. After stirring a few minutes, the suspension colour turned to dark green. 3,3-Dimethylacrylonitrile (5 g, 62 mmol) was added in one portion, followed by methyl bromoacetate (23 mL, 250 mmol), which was added over 1h. After

completion af the addition, the red reaction mixture was cooled, diluted with tetrahydrofuran (550 mL), then with an aqueous 50% potassium carbonate solution (110 mL), and was vigorously stirred for 30 min. The mixture was then filtered through a pad of celite, and the filtrate was concentred *in vacuo*. The residue was taken up with dichloromethane (500 mL), washed with brine, dried (Na_2SO_4), filtered and concentred *in vacuo*. The crude product was purified by chromatography (50% ether/pentane, Rf: 0.7) to give the title product as a yellow oil (5.95 g, 62% yield).
IR (film): ν (cm^{-1}): 3400, 1730, 1650; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 5.58 (1H, s, C_4-H), 4.55 (1H, s, C_2-H), 3.67 (3H, s, OMe), 1.92 (3H, s, Me-C_5), 1.80 (3H, s, C_6-H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 170.8 (CO), 158.4 (C_3), 142.2 (C_5), 121.8 (C_4), 84.7 (C_2), 50.1 (OMe), 26.7 (Me-C_5), 20.1 (C_6); mass (CI NH_3): m/z: 156 (MH^+); high resolution mass spectrum, calculated for $C_8H_{13}NO_2$: 156.1024; found: 156.1022.

(3*S*, 3a *R*, 4a*R*, 5*S*, 8*R*, 8a*S*, 2'*Z*)-[2,2,5,10,10-pentamethyl]-5,8-methanooctahydro-2*H*-isoxazolo-[3,2-*b*]-benzoxazole-3]-3'-yl-3'amino-2'propenoic acid methyl ester (14).

To a suspension of (1*S*)-3-hydroxylamino isoborneol hydrochloride **9** (5 g, 22.5 mmol) in dry dichloromethane (150 mL) was added trimethylorthoformate (10 mL, 90 mmol, 4 eq.). The white suspension was stirred under reflux for 3h30, then flame-dried, powdered 4Á molecular sieves (2 g) were added. After 30 minutes the enaminoester **9** (12.2 g, 80 mmol, 3.5 eq.) was added. The reaction mixture was stirred for further 2h, then cooled to room temperature, filtered through a pad a celite, rinsing with dichloromethane. The filtrate was concentred *in vacuo* and the residue was purified by chromatography (50% ether/pentane) to give the cycloadduct **14** as a yellow anamorphous solid (4.3 g, 54% yield).

IR (film): ν (cm^{-1}): 3400, 1730; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 5.52 (1H, d, J= 5.5 Hz, C_{3a}-H), 4.62 (1H, s, $C_{2'}$-H), 4.13 (1H, d, J= 7.5 Hz, C_{4a}-H), 3.65 (3H, s, OMe), 3.60 (1H, d, J= 7.4 Hz, C_{8a}-H), 2.68 (1H, d, J= 5.5 Hz, C_3-H), 2.08 (1H, d, J= 4.3 Hz, C_8-H), 1.70 (2H, m, C_7-H x 2), 1.45 (3H, s, Me-C_2), 1.30 (3H, s, Me-C_2), 0.90 (2H, m, C_6-H), 1.00, 0.95 and 0.80 (9H, 3s, CH_3 x 3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 170.2 (CO), 158.1 ($C_{3'}$), 101.8 (C_{3a}), 89.9 (C_{4a}), 84.9 ($C_{2'}$), 83,5 (C_2), 78.4 (C_{8a}), 61.7 (C_3), 50.3 (OMe), 49.1 (C_8), 48.4 (C_5), 45.6 (C_{10}), 31.6 (C_6), 27.6 (Me-C_2), 25.5 (C_7), 23.5 (Me-C_2), 22.2, 18.9 and 10.8 (CH_3 x 3); mass (CI NH_3): m/z: 351 (MH^+), 180, 172, 156; $[\alpha]_D^{20}$= + 133 (c= 1, $CHCl_3$); high resolution, calculated for $C_{19}H_{30}N_2O_4$: 351.2283; found: 351.2285.

(3*S*, 3'*S*, 3a *R*, 4a*R*, 5*S*, 8*R*, 8a*S*, 2'*Z*)-[2,2,5,10,10-pentamethyl]-5,8-methanooctahydro-2*H*-isoxazolo-[3,2-*b*]-benzoxazole-3]-3'-yl-3'amino-propionic acid methyl ester (15).

A solution of the cycloadduct **14** (3.32 g, 9.5 mmol) in methanol/dichloromethane (30 mL/60 mL) containing few crystals of bromocresol green was cooled to -90 °C. To this blue solution was added a methanolic 2N hydrogen chloride solution until the colour turned light yellow. A 1N solution of sodium cyanoborohydride in tetrahydrofuran (14.2 mL, 14.2 mmol, 1.5 eq.) was then added dropwise, resulting in a deep blue colour. 30 mL of the methanolic hydrogen chloride solution were then added over 15h (syringe pump). The reaction mixture was slowly warmed to - 20 °C, and an aqueous 0.1N sodium hydroxide solution was added dropwise until a persistant blue colour was obtained. Brine (50 mL) was added and the aqueous phase was extracted with dichloromethane. The combined organic layer was dried (Na_2SO_4), filtered and concentred *in vacuo* to give the amine **15** (3.22 g) as a 92/8 mixture of diastereoisomers which was used immediately into the next reaction.

(3*S*, 3'*S*, 3a *R*, 4a*R*, 5*S*, 8*R*, 8a*S*, 2'*Z*)-[2,2,5,10,10-pentamethyl]-5,8-methanooctahydro-2*H*-isoxazolo-[3,2-*b*]-benzoxazole-3]-3'-yl-3'-phenylmethyloxycarbonylamino-propionic acid methyl ester (16).

N-(Benzyloxycarbonyloxy)-succinimide (2.72 g, 11 mmol, 1.2 eq.) was added in one portion to a solution of the amine **15** (3.22 g, 9.1 mmol) in a mixture od dichloromethane (80 mL) and aqueous 5% sodium hydrogen carbonate solution (80 mL). The biphasic mixture was vigorously stirred at room temperature for 1h, then separated. The aqueous phase was extracted with dichloromethane (50 mL), the combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography (20% ethyl acetate/pentane) to give in order of elution, the major stereomer **16a** (Rf: 0.6, 3.63 g, 78% yield for two steps), followed by the minor stereomer **16b** (Rf: 0.4, 330 mg, 7% yield for two steps).
data for **16a** (white solid): Mp: 133 °C (ether/hexane); IR ($CHCl_3$): ν (cm^{-1}): 3400, 1740; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.35 (5H, broad s, Ar-H), 5.60 (1H, d exchangeable with D_2O, J= 10 Hz, NH), 5.10 (2H, s, $ArCH_2$), 5.00 (1H, d, J= 9.6 Hz, C_{3a}-H), 4.05 (1H, m, $C_{3'}$-H), 3.85 (1H, d, J= 7.5 Hz, C_{4a}-H), 3.70 (3H, s, OMe), 3.35 (1H, d, J= 7.5 Hz, C_8-H), 2.85 (1H, dd, J= 18, 4.4 Hz, $C_{2'}$-H), 2.65 (1H, dd, J= 18, 3.9 Hz, $C_{2'}$-H), 2.45 (1H, dd, J= 11, 8.6 Hz, C_3-H), 2.05 (1H, d, J= 4 Hz, C_8-H), 1.70 (2H, m, C_7-H x 2), 1.40 (2H, m, C_6-H x 2), 1.35 (3H, s, Me-C_2), 1.25 (3H, s, Me-C_2), 0.90, 0.88 and 0.75 (9H, 3s, CH_3 x 3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 172.5 (CO_2Me), 155.4 (CO_2Bn), 136.2, 128.5, 128.0 (Ar), 101.0 (C_{3a}), 87.5 (C_{4a}), 83.9 (C_2), 77.7 (C_{8a}), 66.8 (Ar-CH_2), 53.0 ($C_{3'}$), 51.5 (OMe), 48.6 (C_8), 47.8 (C_5), 46.5 (C_3), 46.1 (C_{10}), 36.6 ($C_{2'}$), 31.4 (C_6), 28.2 (Me-C_2), 25.3 (C_7), 23.1 (Me-C_2), 22.0, 19.3, 10.6 (CH_3 x 3); mass (CI NH_3): m/z: 487 (MH^+), 180; $[\alpha]_D^{20}$= + 66 (c= 1, $CHCl_3$); high resolution mass spectrum (FAB), calculated for $C_{27}H_{38}N_2O_6Na$ (M + Na): 509.2627 found: 509.2623.

(3*S*, 4*S*)-4-carbonyl-5-hydroxy-5-methyl-3-phenylmethyloxycarbonylamino hexanoic acid methyl ester (19).

meta-Chloroperoxybenzoic acid (2.34 g, 7.1 mmol, 5 eq.) was added to a solution of compound **16a** (2.2 g, 4.5 mmol), in anhydrous diethyl ether (70 mL). The clear solution was stirred at room temperature for 15 min and the excess peracid was quenched by the addition of an aqueous 5% sodium thiosulfate/5% sodium hydrogen carbonate solution, followed by vigorous stirring for 30 min. The layers were separated and the aueous layer extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude nitrone **19** as a yellow foam. The crude product was dissolved in tetrahydrofuran (40 mL) and the solution treated with an aqueous 2N hydrochloric acid solution (40 mL). After stirring 15 min at room temperature, the solution was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentred *in vacuo*. The crude product was purified by chromatography (50% ethyl acetate/pentane) to give, in order of elution, the recovered ketol **20** (486 mg), followed by the aldehyde **19** (960 mg, 63% overall yield), which was obtained as a white solid.

IR ($CHCl_3$): ν (cm^{-1}): 3400, 1740, 1720; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 9.85 (1H, d, J= 2.3 Hz, CHO), 7.30 (5H, broad s, Ar-H), 5.90 (1H, d exchangeable with D_2O, J= 8.7 Hz, NH), 5.10 (2H, s, Ar-CH_2), 4.55 (1H, m, C_3-H), 3.60 (3H, s, OMe), 2.85 (1H, dd, J= 16.4, 4.1 Hz, C_2-H), 2.75 (1H, dd, J= 6.1, 2.3 Hz, C_4-H), 2.65, 1H, m, C_2-H), 1.35 (6H, s, CH_3 x 2); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 203.9 (CHO), 171.8 (CO_2Me), 155.6 (CO_2Bn), 136.1, 128.4, 128.0, 127.9 (Ar), 75.1 (C_5), 66.8 ($ArCH_2$), 62.7 (C_3), 51.7 (OMe), 46.4 (C_4), 36.7 (C_2), 29.4, 28.8 (CH_3 x 2); mass (CI NH_3): m/z: 338 (MH^+), 320, 169; $[\alpha]_D^{20}$= -10 (c= 1,4 $CHCl_3$); high resolution mass spectrum (FAB), calculated for $C_{17}H_{23}NO_6Na$ (M + Na): 360.1423 found: 360.1422.

(3*S*, 4*S*)-4-carboxy-5-hydroxy-5-methyl-3-phenylmethyloxycarbonylamino hexanoic acid methyl ester (21).

The aldehyde **19** was dissolved in a mixture of *tert*-butanol (75 mL) and 2-methyl-2-butene (25 mL), and an aqueous 10% sodium chlorite/sodium dihydrogen phosphate solution (26 mL) was added. The reaction mixture was stirred at room temperature for 30 min. Water (300 mL) was added and the solution was extracted with ethyl acetate (5 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentred *in vacuo* to give the crude acid **21** as a white foam, sufficently pure for the next reaction (880 mg).

IR ($CHCl_3$): ν (cm^{-1}): 3500, 3400, 1740, 1722; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.30 (5H, broad s, Ar-H), 6.00 (1H, d exchangeable with D_2O, J= 10 Hz, NH), 5.00 (2H, s, Ar-CH_2), 4.50 (1H, m, C_3-H), 3.65 (3H, s, OMe), 2.65 (3H, m, C_2-H x 2, C_4-H), 1.30 (6H, s, CH_3 x 2); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 176.9 (CO_2H), 172.4 (CO_2Me), 155.8 (CO_2Bn), 136.2,

128.4, 128.0, 127.9 (Ar), 71.1 (C_5), 66.7 ($ArCH_2$), 53.6 (C_3), 51.8 (OMe), 47.1 (C_4), 37.1 (C_2), 29.7, 29.0 (CH_3 x 2); mass (CI NH_3): m/z: 354 (MH^+), 320, 169.

(3*S*, 4*S*)-3-(1-hydroxy-1-methylethyl)-4-methoxycarbonylmethyl-2-azetidinone (22)

To a solution of the crude acid **21** (880 mg, 2.5 mmol) in anhydrous methanol (60 mL) was added 10% palladium on charcoal (880 mg). The black suspension was stirred under an atmosphere of hydrogen for 2h, then filtered through a pad of celite, rinsing with methanol. The filtrate was concentred *in vacuo* to give the free amine (517 mg) as a white solid, which was carried into the next reaction without purification.

This crude compound was dissolved in dry acetonitrile (30 mL), dicyclohexyl carbodiimide (DCC, 976 mg, 4.7 mmol, 2 eq.) was added and the solution stirred at reflux for 2h. After cooling to room temperature, ethyl acetate (30 mL) was added and the solution filtered. The filtrate was concentred *in vacuo* and the residue purified by chromatography (10% methanol/ethyl acetate, Rf: 0.6) to give the β-lactam **22** as a colourless oil (248 mg, 48% yield from aldehyde **19**).

IR ($CHCl_3$): ν (cm^{-1}): 3400, 1740, 1735; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 6.30 (1H, s, exchangeable with D_2O, NH), 4.10 (1H, ddd, J= 8.6, 5.3, 3.2 Hz, C_4-H), 3.70 (3H, s, OMe), 3.30 (2H, m, C_3-H and one of CH_2CO_2), 2.90 (1H, dd, J= 17.2, 3.2 Hz, one of CH_2CO_2), 1.90 (1H, s, exchangeable with D_2O, OH), 1.53 and 1.28 (6H, 2s, CH_3 x 2); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 172.6 (CO_2), 168.3 (CO), 70.1 (C-OH), 62.4 (C_4), 51.9 (OMe), 48.5 (C_3), 35.2 (CH_2CO_2), 29.9, 28.3 (CH_3 x 2); mass (CI NH_3): m/z: 219 (MNH_4^+), 202 (MH^+), 187, 141; $[\alpha]_D^{20}$= -108 (c= 0.5, $CHCl_3$); elemental analysis, calculated for $C_9H_{15}NO_4$, MW: 201.2242; calc.: C: 53.72%; H: 7.51%; N: 6.96%; found: C: 53.99%; H: 7.47%; N: 6.77.

(3*S*, 4*S*)-3-(1-methyl-1-trimethylsilyloxyethyl)-4-methoxycarbonylmethyl-2-azetidinone (23a).

A solution of the azetidinone **23** (248 mg, 1.23 mmol) and 4-dimethylaminopyridine (23 mg, 1.85 mmol, 0.15 eq.) in anhydrous tetrahydrofuran (15 mL) was cooled to 0 °C. Freshly distilled triethylamine (1.1 mL, 8.63 mL, 7 eq.) was slowly added, followed by freshly distilled trimethylsilyl chloride (1.2 mL, 8.6 mmol, 7 eq.). The resulting white suspension was stirred at room temperature for 12 h then filtered through a short pas of celite. The filtrate was concentred *in vacuo* and the residue purified by chromatography (10% methanol/dichloromethane) to give in order of elution, the *bis*-silylated product **23b** (44 mg, 10% yield), followed by the *O*-silylated product **23a** (232 mg, 69% yield), which was obtaine as a white solid.

IR ($CHCl_3$): ν (cm^{-1}): 3400, 1740, 1735; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 6.30 (1H, s, exchangeable with D_2O, NH), 4.10 (1H, ddd, J= 8.6, 5.3, 3.2 Hz, C_4-H), 3.70 (3H, s, OMe), 3.30 (2H, m, C_3-H and one of CH_2CO_2), 2.90 (1H, dd, J= 17.2, 3.2 Hz, one of CH_2CO_2), 1.53 and

1.28 (6H, 2s, CH_3 x 2), 0.15 (9H, s, $(CH_3)_3Si$; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 172.7 (CO_2), 168.3 (CO), 72.8 (C-OSi), 63.7 (C_4), 51.7 (OMe), 48.4 (C_3), 35.2 (CH_2CO_2), 29.7, 28.7 (CH_3 x 2), 2.3 ($(CH_3)_3Si$); mass (CI NH_3): m/z: 274 (MH^+), 141; $[\alpha]_D^{20}$= -65 (c= 1, $CHCl_3$); high resolution mass spectrum (FAB), calculated for $C_{12}H_{23}NO_4NaSi$, (M+ Na): 296.1294; found: 296.1304.

(3*S*, 4*S*)-3-(1-methyl-1-trimethylsilyloxyethyl)-4-carboxymethyl-2-azetidinone (24).

A solution of the azetidinone **24a** (69 mg, 0.2 mmol) in 4/1 methanol/water (1.5 mL) was treated with an aqueous 2.5 N sodium hydroxide solution (102 μL). After stirring 3h at room temperature, ether was added and the layers separated. The aqueous layer was acidified to pH 5 by careful addition of aqueous 2N hydrochloric acid solution with vigorous stirring. The solution was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentred *in vacuo* to give the carboxylic acid **25** as white droplets (32 mg, 64% yield).

IR ($CHCl_3$): ν (cm^{-1}): 3400, 1730, 1710; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.55 (1H, s, exchangeable with D_2O, NH), 4.01 (1H, ddd, J= 11.6, 5.2, 2.5 Hz, C_4-H), 3.32 (1H, dd, J= 17.2, 11.6 Hz, one of CH_2CO_2), 3.17 (1H, dd, J= 5.2, 0.8 Hz, C_3-H), 2.78 (1H, dd, J= 17.2, 2.5 Hz, one of CH_2CO_2), 1.53, 1.30 (6H, 2s, CH_3 x 2), 0.15 (9H, s, $(CH_3)_3Si$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 175.9 (CO_2H), 171.2 (CO), 72.8 (C-OH), 63.4 (C_4), 49.3 (C_3), 34.6 (CH_2CO_2), 29.7, 28.9 (CH_3 x 2), 2.4 ($(CH_3)_3Si$); mass (CI NH_3): m/z: 260 (MH^+); $[\alpha]_D^{20}$= -53 (c= 0.3, acetone); lit. (enantiomer)[3d]: + 53 (c= 1.5, acetone); high resolution mass spectrum (FAB), calculated for $C_{11}H_{21}NO_4NaSi$, (M+ Na): 282.1137; found: 282.1131.