Supporting Information for:
Enantioselective Synthesis of Functionalized Medium-Sized Oxacycles

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(Z,5S,6R)-2-Ethylidene-4,5-dimethyl-6-phenylmorpholin-3-one (2):¹

To a suspension of the dione **1** (2.87 g, 13.2 mmol) in ether (25 mL) was added ethylmagnesium bromide (prepared from magnesium metal (0.74 g, 30 mmol) and ethyl iodide (2.22 mL, 27 mmol) in ether (10 mL)) at 0 °C and the mixture was stirred at room temperature for 3 h. A saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried (Na₂SO₄) and concentrated to provide 3.2 g (98%) of the hemiacetal. This was dissolved in dichloromethane (60 mL), the solution was cooled to -78 °C and BF₃ etherate (5 mL, 38.5 mmol) was added. The solution was stirred at room temperature for 18 h. and cold water (35 mL) was added. The mixture was extracted with dichloromethane (3 x 30 mL) and the combined extracts were dried (Na₂SO₄) and concentrated to provide the crude product. Purification by flash chromatography on silica gel (2/1 ethyl acetate/hexane) furnished 2.9 g (95% over 2 steps) of **2** as a pale yellow gum. Spectroscopic data for **2** was identical to the reported data.¹

(2S,3S,5R,6S)-5-Phenyl-2,6,7-trimethyl-1,4,dioxo-7-azaspiro[2,5]octan-8-one (3):

To a solution of **2** (1 g, 4.3 mmol) in dichloromethane (15 mL) was added *m*CPBA (1.2 g, 6.9 mmol) at -78 °C and the mixture was warmed to room temperature and stirred for 45 min. Saturated NaHCO₃ solution was added and the mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel (ethyl acetate) to give 860 mg (80 %) of **3** as a white, crystalline solid.

Mp: 141-142 °C; IR (solid): 2360, 2344, 1665, 1291, 923, 891 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.39-7.36 (m, 2H, ArH), 7.33-7.30 (m, 3H, ArH), 5.48 (d, 1H, $J = 2.2$ PhCH), 3.84 (q, 1H, $J = 5.2$, OCHCH₃), 3.64 (dq, 1H, $J = 3.5, 6.3$, NCHCH₃), 3.10 (s, 3H, NCH₃), 1.51 (d, 3H, $J = 5.2$, OCHCH₃), 1.03 (d, 3H, $J = 6.3$, NCHCH₃). ^{13}C NMR (125.77 MHz, CDCl_3): δ 163.4, 136.6, 128.5, 128.1, 125.4, 82.0, 75.9, 59.2, 58.5, 33.8, 12.8, 12.4; $[\alpha]_D^{23} = -161.9$ (c 1, CH_2Cl_2); MS (APCI): 248.1 (M+1, 100); HRMS (CI): m/z 247.1202 (247.1208 calc. for $\text{C}_{14}\text{H}_{17}\text{NO}_3$, M+).

(2*S*,5*S*,6*R*)-2-Allyl-2-((*S*)-1-hydroxyethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (4):

To a solution of **3** (770 mg, 3.1 mmol) in dichloromethane (25 ml) at -78 °C was added allyltrimethylsilane (3.0 ml, 18.6 mmol) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.3 ml, 18.6 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 3 h. Cold water was added and the resulting mixture was extracted with dichloromethane (3 x 25 ml). The combined organic layers were concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (2/1 ethyl acetate/hexane) to provide 360 mg (40%) of **4** as a white solid.

IR (solid): 3394, 2974, 2936, 2896, 1622, 978, 887 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.40-7.37 (m, 2H, ArH), 7.33-7.27 (m, 3H, ArH), 5.95 (m, 1H, CH=CH₂), 5.41 (d, 1H, $J = 2.2$, PhCH), 5.17 (dd, 1H, $J = 1.4, 16.1$, CH=CH₂), 5.05 (d, 1H, $J = 10.3$, CH=CH₂), 4.05 (dq, 1H, $J = 6.5, 2.7$, OCHCH₃), 3.88 (d, 1H, $J = 2.7$, OH), 3.52 (dq, 1H, $J = 6.6, 2.2$, NCHCH₃), 3.06 (s, 3H, NCH₃), 2.96 (m, 1H, CH₂CH), 2.65 (dd, 1H, $J = 7.9, 14.9$, CH₂CH), 1.37 (d, 3H, $J = 6.5$, OCHCH₃), 0.98 (d, 3H, $J = 6.6$, NCHCH₃). ^{13}C NMR (125.77 MHz, CDCl_3): δ 171.6, 137.9, 134.3, 128.6, 127.9, 125.7, 118.4, 81.9, 73.2, 72.0, 59.3, 37.0, 33.9, 16.9, 13.0; MS (APCI): 290.1 (M+1, 100); HRMS (CI): m/z 289.1669 (289.1678 calc. for $\text{C}_{17}\text{H}_{23}\text{NO}_3$, M+).

(2*S*,5*S*,6*R*)-2-Allyl-2-((*S*)-1-(allyloxy)ethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (5):

To a solution of the alcohol **4** (300 mg, 1.04 mmol) in THF (15 ml) at 0 °C was added KH (50 mg, 1.25 mmol). The mixture was stirred at 0 °C for 15 min and allyl bromide (0.27 ml, 3.12 mmol) was added dropwise. The mixture was then warmed up to ambient temperature, stirred for 3.5 h and cold water was added. The mixture was extracted with ethyl acetate (3 x 20ml) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2/1 ethyl acetate/hexane) to provide 300 mg (88 %) of **5** as a yellow gum.

IR (neat): 2980, 1636, 1451, 1379, 1071, 1030, 919 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.39-7.29 (m, 5H, ArH), 6.0-5.91 (m, 2H, $\text{CH}=\text{CH}_2$, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.31-5.26 (m, 2H, $\text{OCH}_2\text{CH}=\text{CH}_2$, PhCH), 5.17-5.02 (m, 3H, $\text{OCH}_2\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}_2$), 4.20-4.16 (m, 1H, OCH_2), 4.10-4.06 (m, 1H, OCH_2), 3.81 (q, 1H, $J = 6.5$, OCHCH_3), 3.50-3.47 (dq, 1H, $J = 6.1$, 2.9, NCHCH_3), 3.04 (s, 3H, NCH_3), 2.83 (dd, 1H, 2.6, 6.5, CCH_2CH), 2.72 (dd, 1H, $J = 6.5$, 6.7, CCH_2CH), 1.37 (d, 3H, $J = 6.5$, OCHCH_3), 1.02 (d, 3H, $J = 6.1$, NCHCH_3); ^{13}C NMR (125.77 MHz, CDCl_3): δ 169.6, 138.5, 135.6, 133.8, 128.5, 127.7, 125.9, 118.0, 116.9, 84.6, 79.9, 72.4, 71.7, 59.3, 38.8, 34.0, 15.4, 12.9; MS (APCI): 330.2 ($\text{M}+1$, 100); HRMS (CI): m/z 329.1982 (329.1991 calc. for $\text{C}_{20}\text{H}_{27}\text{NO}_3$, $\text{M}+$).

(2*R*,3*S*,6*S*,7*S*)-2-Phenyl-3,4,7-Trimethyl-1,8-dioxaspiro[5.6]dodec-10-en-5-one (6):

To a solution of **5** (220 mg, 0.67 mmol) in dichloromethane (90 ml) was added Grubbs I catalyst (25 mg, 0.03 mmol, 4.5 mol %). The mixture was stirred at room temperature for 5 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give 140 mg (70 %) of **6** as pale yellow oil.

IR (neat): 2938, 1628, 1448, 1402, 1380, 1027, 900 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.37-7.36 (m, 4H, ArH), 7.30-7.27 (m, 1H, ArH), 5.71-5.68 (m, 1H, $\text{CH}=\text{CH}$), 5.65-5.62 (m, 1H, $\text{CH}=\text{CH}$), 5.16 (d, 1H, $J = 3.5$, PhCH), 4.34-4.46 (m, 2H, OCH_2CH , OCHCH_3), 4.26-4.22 (m, 1H, OCH_2CH), 3.53 (dq, 1H, $J = 6.1$, 3.4, NCHCH_3), 3.01 (s, 3H, NCH_3), 2.89 (dq, 2H, $J = 6.6$, 4.7, CCH_2CH), 1.31 (d, 3H, $J = 6.2$, OCHCH_3), 0.97 (d, 3H, $J = 6.1$, NCHCH_3); ^{13}C NMR (125.77 MHz, CDCl_3): δ 170.5, 138.2, 130.5, 128.5, 127.7, 125.7, 125.4, 83.8, 80.7, 71.2, 69.1, 59.1, 33.9, 33.8, 16.8, 13.4; MS (APCI): 302.1 ($\text{M}+1$, 100); HRMS (CI): m/z 301.1670 (301.1678 calc. for $\text{C}_{18}\text{H}_{23}\text{NO}_3$, $\text{M}+$).

(*Z*,2*S*,3*S*)-2,3,4,7-Tetrahydro-3-hydroxy-*N*,2-dimethyloxepine-3-carboxamide (7):

To anhydrous liquid ammonia (distilled over sodium) was added Na metal (64 mg, 2.79 mmol) at -78°C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **6** (120 mg, 0.4 mmol) in anhydrous THF (2.5 ml) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3ml) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (3/2, ethyl acetate/hexane) to provide 35 mg (47%) of **7** as a white solid.

IR (neat): 3435, 3015, 1737, 1686, 1537, 1215, 745 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 6.91 (s, 1H, NHCO), 5.96-5.91 (m, 1H, $\text{CH}=\text{CH}$), 5.76-5.71 (m, 1H, $\text{CH}=\text{CH}$), 4.32 (dd, 1H, $J = 9.6, 5.8$, OCH_2CH), 4.12 (m, 1H, OCH_2CH), 3.98 (q, 1H, $J = 6.3$, OCHCH_3), 3.12 (s, 1H, OH), 2.94 (m, 1H, CCH_2CH), 2.83 (d, 3H, $J = 4.3$, NHCH_3), 2.46 (dd, 1H, $J = 16.7, 8.1$, CCH_2CH), 1.12 (d, 3H, $J = 6.3$, CH_3CHO); ^{13}C NMR (125.77 MHz, CDCl_3): δ 174.1, 131.3, 128.3, 82.6, 76.4, 69.2, 38.9, 25.8, 17.4; 186.1 ($\text{M}+1$, 100); $[\alpha]_D^{23} = 53.6$ (c 1, CH_2Cl_2); HRMS (CI): m/z 185.1043 (185.1052 calc. for $\text{C}_9\text{H}_{15}\text{NO}_3$, M^+).

(2*S*,5*S*,6*R*)-2-((*S*)-1-(3-Methylbut-3-enyloxy)ethyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (8):

To a solution of 3-methyl-3-butene-1-ol (442 ml, 4.4 mmol) in THF (35 ml) at 0 °C was added NaH (121 mg, 5.04 mmol). The mixture was then stirred for 15 min at 0 °C and the epoxide **3** (900 mg, 3.6 mmol) was added as a solid. The reaction mixture was warmed up to ambient temperature, stirred for 3 h, cold water was added, and the mixture was extracted with ethyl acetate (3 x 20ml). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 1 g (83 %) of **8** as a colorless gum.

IR (neat): 3347, 2940, 1641, 1452, 1109, 1024, 891 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.37-7.33 (m, 4H, ArH), 7.31-7.27 (m, 1H, ArH), 5.38 (d, 1H, $J = 2.6$, PhCH), 4.71 (s, 1H, $\text{C}=\text{CH}_2$), 4.67 (s, 1H, $\text{C}=\text{CH}_2$), 4.04 (s, 1H, OH), 3.88 (q, 1H, $J = 6.4$, OCHCH_3), 3.67 (m, 1H, OCH_2), 3.46-3.41 (m, 2H, NCHCH_3 , OCH_2), 3.02 (s, 3H, NCH_3), 2.23-2.20 (m, 2H, CH_2C), 1.70 (s, 3H, CCH_3), 1.36 (d, 3H, $J = 6.4$, OCHCH_3), 1.03 (d, 3H, $J = 6.2$, NCHCH_3); ^{13}C NMR (125.77 MHz, CDCl_3): δ 168.8, 143.0, 137.8, 128.5, 127.8, 126.1, 111.5, 97.6, 79.2, 72.9, 68.3, 59.8, 38.4, 33.7, 22.7, 12.1, 12.0; MS (APCI): 334.2 ($\text{M}+1$, 100); HRMS (CI): m/z 333.1933 (333.1940 calc. for $\text{C}_{19}\text{H}_{27}\text{NO}_4$, M^+).

(2*S*,5*S*,6*R*)-2-Hydroxy-4,5-dimethyl-6-phenyl-2-((*S*)-1-(prop-2-ynyloxy)ethyl)morpholin-3-one (9):

To a solution of propargyl alcohol (0.2 ml, 3.4 mmol) in THF (15 ml) at 0 °C was added NaH (190 mg, 7.94 mmol). The reaction mixture was stirred at 0 °C for 15 min and the epoxide **3** (700 mg, 2.83 mmol) was added as a solid. The reaction mixture was warmed up to ambient temperature, stirred for 2.5 h and cold water was added. The mixture was extracted with ethyl

acetate (3 x 15ml) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 650 mg (76%) of **9** as a white solid.

Mp: 133-134 °C; IR (solid): 3294, 1658, 1449, 1195, 1148, 1078, 1014, 967 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.37-7.32 (m, 4H, ArH), 7.28-7.26 (m, 1H, ArH), 5.42 (d, 1H, $J = 2.7$, PhCH), 5.1 (s, 1H, OH), 4.18-4.12 (d of AB, 2H, $J = 15, 2$, OCH_2), 4.07 (q, 1H, $J = 6.5$, OCHCH_3), 3.44-3.40 (dq, $J = 2.7, 7.1$, NCHCH_3), 3.01 (s, 3H, NCH_3), 2.39 (t, 1H, $J = 2$, $\text{CH}_2\text{C}\equiv\text{CH}$), 1.43 (d, 3H, $J = 6.5$, OCHCH_3), 1.03 (d, $J = 7.1$, NCHCH_3). ^{13}C NMR (125.77 MHz, CDCl_3): δ 168.9 ($\text{C}=\text{O}$), 137.7, (ArC_{ipso}), 128.4 (ArC), 127.8 (ArC), 126 (ArC), 97.2 (OC_{quat}), 80.3 (OCH_2C), 78.8 (OCH), 74 ($\text{C}\equiv\text{CH}$), 72.4 (PhCH), 59.6 (NCH_3), 57.7 ($\text{C}\equiv\text{CH}$), 33.8 (NCHCH_3), 12.7 (OCHCH_3), 12 (NCHCH_3); MS (APCI): 304.1 ($\text{M}+1$, 100); HRMS (CI): m/z 303.1481 (303.1471 calc. for $\text{C}_{17}\text{H}_{21}\text{NO}_4$, M^+).

(2*S*,5*S*,6*R*)-2-((*R*)-1-(3-Methylbut-3-enyloxy)ethyl)-2-allyl-4,5-dimethyl-6-phenylmorpholin-3-one (10**):**

To a solution of **8** (500 mg, 1.5 mmol) in dichloromethane (20 ml) at -78 °C was added allyltrimethylsilane (1.5 ml, 9 mmol) followed by $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.1 ml, 9 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 36 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 20ml). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 232 mg (43%, 63% based on recovered starting material (160 mg)) of **10** as a colorless oil.

IR (neat): 2982, 1737, 1605, 1402, 1310, 1166, 1090, 1068, 852 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.38-7.34 (m, 4H, ArH), 7.30-7.27 (m, 1H, ArH), 6.02-5.96 (m, 1H, $\text{CH}=\text{CH}_2$), 5.30 (d, 1H, $J = 2.5$, PhCH), 5.09 (dd, 1H, $J = 13.3, 1.0$, $\text{CH}=\text{CH}_2$), 4.70 (d, 1H, $J = 10.1$, $\text{CH}=\text{CH}_2$), 4.72 (s, 1H, $\text{C}=\text{CH}_2$), 4.67 (s, 1H, $\text{C}=\text{CH}_2$), 3.81 (q, 1H, $J = 6.3$, OCHCH_3), 3.68-3.63 (m, 1H, OCH_2), 3.46-3.40 (m, 2H, NCHCH_3 , OCH_2), 3.02 (s, 3H, NCH_3), 2.63 (dd, 1H, $J = 14.1, 7.4$, CCH_2CH), 2.53 (dd, 1H, $J = 14.1, 7.2$, CCH_2CH), 2.21 (brt, 2H, $J = 6.5$, OCH_2CH_2), 1.72 (s, 3H, CCH_3), 1.32 (d, 3H, $J = 6.3$, OCHCH_3), 1.01 (d, 3H, $J = 6.2$, NCHCH_3); ^{13}C NMR (125.77 MHz, CDCl_3): δ 170.1, 143.2, 138.9, 134.5, 128.4, 127.6, 126.0, 117.8, 111.4, 84.0, 80.4, 73.4, 68.4, 59.5, 40.8, 38.5, 33.8, 22.8, 13.0, 12.2; MS (APCI): 358.3 ($\text{M}+1$, 100); HRMS (CI): m/z 357.2305 (357.2304 calc. for $\text{C}_{22}\text{H}_{31}\text{NO}_3$, M^+).

(2*S*,5*S*,6*R*)-2-Allyl-4,5-dimethyl-6-phenyl-2-((*R*)-1-(prop-2-ynyloxy)ethyl)morpholin-3-one (11):

To a solution of **9** (430 mg, 1.42 mmol) in dichloromethane (20 ml) at -78 °C was added allyltrimethylsilane (1.35 ml, 8.52 mmol) followed by BF₃.Et₂O (1.1 ml, 8.52 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 3 days. Cold water was added and the resulting mixture was extracted with dichloromethane (3 x 20ml). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 60 mg (43% based on recovered starting material (300 mg)) of **11** as a colorless oil.

IR (solid): 1703, 1580, 1421, 1389, 1135, 1054, 1010 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.34 (m, 4H, ArH), 7.29-1.27 (m, 1H, ArH), 6.01-5.93 (m, 1H, CH=CH₂), 5.32 (d, 1H, *J* = 2.6, PhCH), 5.10 (d, 1H, *J* = 16.6, 1H, CH=CH₂), 5.16 (d, 1H, *J* = 10, 1H, CH=CH₂), 4.19-4.10 (d of AB, 2H, *J* = 16, 2, OCH₂C), 3.96 (q, 1H, *J* = 6.5, NCHCH₃), 3.40 (dq, *J* = 2.6, 7.2, NCHCH₃), 3.03 (s, 3H, NCH₃), 2.65-2.61 (dd, 1H, *J* = 14, 7.2, CH₂CH=CH₂), 2.53-2.50 (dd, 1H, *J* = 14, 7.2, CH₂CH=CH₂), 2.36 (br t, 1H, *J* = 2, CH₂C≡CH), 1.38 (d, 3H, *J* = 6.5, NCHCH₃), 1.04 (d, *J* = 7.2, OCHCH₃); ¹³C NMR (125.77 MHz, CDCl₃): δ 169.8, 138.7, 128.4, 127.7, 126.0, 118.0, 83.9, 80.8, 80.7, 80.6, 73.6, 73.4, 59.9, 40.7, 40.5, 33.9; MS (APCI): 328.3 (M+1, 100); HRMS (CI): *m/z* 327.1835 (327.1834 calc. for C₂₀H₂₅NO₃, M+).

(2*R*,3*S*,6*S*,7*S*)-3,4,7,11-Tetramethyl-2-phenyl-1,8-dioxo-4-azaspiro[5.7]tridec-11-en-5-one (12):

To a solution of **10** (100 mg, 0.28mmol) in dichloromethane (28 ml) was added the Grubbs II catalyst (56 mg, 0.07 mmol, 20 mol %). The reaction mixture was stirred at room temperature for 48 h and the solvent was removed under pressure. The residue was purified by flash chromatography on silica gel to give 80 mg (87 %) of **12** as a colorless oil.

IR (neat): 2933, 1642, 1450, 1111, 1093, 959, 900, 847 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.39-7.28 (m, 5H, ArH), 5.25 (br, 2H, PhCH, CH=C), 4.17 (br dt, 1H, *J* = 12.0, 2.8, CH₂O), 3.58 (q, 1H, *J* = 6.3, OCHCH₃), 3.51 (dq, 1H, *J* = 6.7, 3.1, NCHCH₃), 3.41 (t, 1H, *J* = 12.0, CH₂O), 3.17 (dd, 1H, *J* = 14, 10.4 CH₂), 3.01 (s, 3H, NCH₃), 2.89 (br t, 1H, *J* = 12, CH₂), 2.60 (dd, 1H, *J* = 5.8, 14, CH₂), 1.78 (s, 3H, CH₃C), 1.75 (dd, 1H, *J* = 12.2, 2.8, CH₂), 1.19 (d, 3H, *J* = 6.3, OCHCH₃), 0.92 (d, 3H, *J* = 6.7, CH₃CHCH). ¹³C NMR (125.77 MHz, CDCl₃): 158.9, 145.4,

136.7, 128.6, 128.2, 125.5, 111.9, 77.5, 66.2, 58.6, 58.1, 33.7, 11.8; MS (APCI): 330.2 (M+1, 100); HRMS (CI): m/z 329.1993 (329.1991 calc. for C₂₀H₂₇NO₃, M+).

(Z,2R,3S)-3,4,7,8-Tetrahydro-3-hydroxy-N,2,6-trimethyl-2H-oxocine-3-carboxamide (13):

To anhydrous liquid ammonia (distilled over sodium) was added Na metal (38 mg, 1.66 mmol) at -78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **12** (78 mg, 0.24 mmol) in anhydrous THF (2.5 ml) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3ml) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (ethyl acetate) to provide 40 mg (79%) of **13** as a white solid.

Mp: 102-103 °C; IR (solid): 3354, 2920, 1700, 1684, 1540, 1088, 968, 895 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.72 (br s, 1H, NHCO), 5.32 (br s, 1H, CH=C), 4.22 (br s, 1H, CH₂O), 4.01 (br s, 1H, CH₂O), 4.68 (br q, 1H, OCHCH₃), 3.53 (br t, 1H, CH₂), 2.89 (d, 3H, J = 5.4, NHCH₃), 2.75 (br s, 2H, CH₂), 2.17 (br s, 1H, CH₂), 1.84 (br s, 4H, OH, CCH₃), 1.02 (d, 3H, J = 6.3, OCHCH₃); a satisfactory ¹³C spectrum could not be obtained due to atropisomerism resulting in peak broadening. [α]_D²³ = -109 (c 1, CH₂Cl₂); MS (APCI): 214.1 (M+1, 100); HRMS (CI): m/z 213.1371 (213.1365 calc. for C₁₁H₁₉NO₃, M+).

(1S,2S,6R,7S)-2-Bromo-7-hydroxy-2,6-dimethyl-5,9-dioxabicyclo[5.2.1]decan-8-one (14):

To a solution of **13** (40 mg, 0.19 mmol) in THF (1 mL) was added *N*-bromosuccinimide (50 mg, 0.28 mmol) and the solution was stirred for 3 h at room temperature. Saturated aqueous NaHSO₃ solution (1.5 ml) was added and the mixture was extracted with ethyl acetate (3 x 3 ml). The combined organic layers were dried (Na₂SO₄), concentrated and the residue was purified by flash chromatography on silica gel (7/3 ethyl acetate/hexane) to give 27 mg (54%) of **14** as a colorless gum.

¹H NMR (500 MHz, CDCl₃): δ 4.77 (dd, 1H, J = 11.5, 1.5, CHC(O)), 4.12 (ddd, 1H, J = 13, 6, 2, CH₂O), 3.8 (dd, 1H, J = 13, 9, CH₂O), 3.76 (q, 1H, J = 6.3, OCHCH₃), 3.20 (dd, 1H, J = 15.5, 2, CH₂), 2.78 (dd, 1H, J = 15.5, 11, CH₂), 2.72 (br s, 1H, OH), 2.36 (ddd, 1H, J = 16.5, 10, 2 CH₂), 2.25 (dd, 1H, J = 16.5, 6, CH₂), 1.95 (s, 3H, CH₃CBr), 1.37 (d, 3H, J = 6.3, OCHCH₃). ¹³C NMR (125.77 MHz, CDCl₃): δ 177.7 (C=O), 83.5 (CO₂CH), 81.4 (OCHCH₃), 76.4 (OCH₂), 68.6 (C(OH)C(O)), 67.7 (CBr), 44.4 (CH₂), 38.8 (CH₂), 34.2 (CH₃), 15.9 (CH₃).

(2R,3S,6S,7S)-3,4,7-Trimethyl-2-phenyl-10-vinyl-1,8-dioxa-4-azaspiro[5.6]dodec-10-en-5-one (15):

To a solution of **11** (50 mg, 0.15 mmol) in dichloromethane (15 ml) was added Grubbs I catalyst (15 mg, 0.02 mmol, 10 mol%). The mixture was stirred at room temperature for 48 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give 45 mg (90%) of **15** as colorless oil.

IR (neat): 1646, 1452, 1399, 1380, 1253, 1146, 1123, 1097, 991 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.39-7.28 (m, 5H, ArH), 6.23 (dd, 1H, $J = 9.2, 6.9$, $\text{CH}_2\text{CH}=\text{C}$), 5.61 (t, $J = 6.4$, $\text{CH}_2\text{CH}=\text{C}$), 5.16 (d, 1H, $J = 3.6$, PhCH), 4.93 (d, 1H, $J = 13$, $\text{C}=\text{CH}_2$), 4.90 (d, 1H, $J = 18.5$, $\text{C}=\text{CH}_2$), 4.78 (br d, 2H, $\text{OCH}_2\text{C}=\text{CH}$), 4.54 (dd, 1H, $J = 13.3, 2.6$, $\text{OCH}_2\text{C}=\text{CH}$), 3.79 (q, 1H, $J = 6.8$, OCHCH_3), 3.51 (dq, $J = 3.6, 6.5$, 1H, NCHCH_3), 3.47-3.44 (m, 1H, $\text{CH}_2\text{CH}=\text{C}$), 3.0 (s, 3H, NCH_3), 2.60 (q, 1H, $J = 15, 9$, $\text{CH}_2\text{CH}=\text{C}$), 1.28 (d, 1H, $J = 6.8$, OCHCH_3), 0.95 (3H, $J = 6.5$, NCHCH_3); ^{13}C NMR (125.77 MHz, CDCl_3): δ 169.6, 138.03, 138.01, 128.5, 127.8, 127.0, 125.8, 111.4, 89.3, 79.5, 72.8, 72.3, 59.0, 33.7, 30.5, 17.0, 12.5; $[\alpha]_D^{23} = 24$ (c 1, CH_2Cl_2); MS (APCI): 328.3 ($\text{M}+1$, 100); HRMS (CI): m/z 327.1834 (327.1834 calc. for $\text{C}_{20}\text{H}_{25}\text{NO}_3$, M^+).

(5R,6R,8R,9S)-8-Phenyl-5,9,10-Trimethyl-1,3,7-trioxa-10-azaspiro[5,5]undecan-11-one (17):

To a solution of **2** (562 mg, 2.4 mmoles) in glacial acetic acid (10 ml) was added formaldehyde (406 mg, 13.5 mmoles) and H_2SO_4 (0.1 ml). The reaction mixture was stirred at 85 $^\circ\text{C}$ for 8 hrs and saturated NaHCO_3 solution was added and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (2/3 ethyl acetate/hexanes) to provide 340 mg (45%) of **17** as a white solid.

Mp: 134-135 $^\circ\text{C}$. IR (neat): 2977, 1756, 1663, 1153, 985, 967, 881 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.44-7.28 (m, 5H, ArH), 5.51 (d, 1H, $J = 3.5$, PhCH), 4.81 (d, 1H, $J = 5.8$, OCH_2O), 5.04 (d, 1H, $J = 5.8$, OCH_2O), 3.90 (dd, $J = 11, 5$, CHCH_2O), 3.80 (t, $J = 11$, CHCH_2O), 3.54 (dq, 1H, $J = 6.1, 3.5$, NCH), 3.07 (s, 3H, NCH_3), 3.01 (m, 1H, CH_3CHCH_2), 0.99 (d, 1H, $J = 6.1$, CH_3CHN), 0.89 (d, 1H, $J = 6.7$, CH_3CHCH_2); ^{13}C NMR (125.77 MHz, CDCl_3): δ 164.7 ($\text{C}=\text{O}$), 137.4 (ArC_{ipso}), 128.8 (ArCH), 128.1 (ArCH), 125.6 (ArCH), 100 (OC_{quat}), 96.8 (OCH_2O), 70.4 (OCH_2C), 68.1 (PhCH), 59.2 (NCH_3), 34.7 (NCH), 34.1 (CH_2CHCH_3), 13 (CH_3), 11.7 (CH_3); $[\alpha]_D^{23} = -47.3$ (c 1, CH_2Cl_2); MS (APCI): 292.1 ($\text{M}+1$, 100); HRMS (CI): m/z 291.1472 (291.1471 calc. for $\text{C}_{16}\text{H}_{21}\text{NO}_4$, M^+).

(2*S*,5*S*,6*R*)-2-Allyl-2-((*S*)-1-(but-3-enyloxy)propan-2-yl)-4,5-dimethyl-6-phenylmorpholin-3-one (18):

To a solution of **17** (310 mg, 1.06 mmol) in dichloromethane (3.5 ml) at -78 °C was added allytrimethylsilane (3.4 ml, 21.2 mmol) followed by BF₃.Et₂O (2.65 ml, 21.2 mmol). The mixture was stirred at -78 °C for 15 min and then at ambient temperature for 96 h. Cold water was added and the resulting mixture was extracted with dichloromethane (3 x 20ml). The combined organic layers were dried, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 290 mg (76%) of **18** as a yellow oil.

IR (neat): 2978, 1643, 1452, 1398, 1378, 1246, 1103, 1001, 913 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.38-7.27 (m, 5H, ArH), 5.99-5.94 (m, 1H, CH=CH₂), 5.87-5.81 (m, 1H, CH=CH₂), 5.32 (d, 1H, *J* = 2.7, PhCH), 5.09 (d, 2H, *J* = 16.8, CH=CH₂), 5.02 (d, 2H, *J* = 10.5, CH=CH₂), 3.84 (dd, 1H, *J* = 4.9, 2.1, (OCH₂), 3.54-3.40 (m, 4H, NCH, CHCH₂O, OCH₂CH₂), 3.01 (s, 3H, NCH₃), 2.80 (dd, 1H, *J* = 7, 14.6, CH₂CH=CH₂), 2.72 (dd, 1H, *J* = 7, 14.6, CH₂CH=CH₂), 2.44-2.41 (m, 1H, CH₂CH₂CH=CH₂), 2.36-2.32 (m, 2H, CH₂CH₂CH=CH₂, CH₃CHCH₂), 1.20 (d, 1H, *J* = 6.5, CH₃CHCH₃), 0.94 (d, 1H, *J* = 6.8, CH₃CHCH₂); ¹³C NMR (125.77 MHz, CDCl₃): δ 170.7, 138.4, 135.7, 134.4, 128.5, 127.7, 125.7, 117.7, 116.3, 82.9, 71.7, 71.6, 70.4, 60.6, 59.2, 40.7, 40.3, 34.5, 33.8, 14.4, 14.2, 13.2; MS (APCI): 358.3 (M+1, 100); HRMS (CI): *m/z* 357.2300 (357.2304 calc. for C₂₂H₃₁NO₃, M+).

(*Z*,3*R*,4*S*)-2,3,4,5,8,9-Hexahydro-4-hydroxy-*N*,3-dimethylloxonine-4-carboxamide (19):

To anhydrous liquid ammonia (distilled over sodium) was added Na metal (59 mg, 2.5 mmol) at -78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of ring closing metathesis product obtained from **18** (40 mg, 0.12 mmol) in anhydrous THF (2.5 ml) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3ml) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (3/2, ethyl acetate/hexane) to provide 23 mg (89%) of **19** as a white solid.

IR (neat): 3422, 2936, 2866, 1656, 1650, 1562, 1121, 958, 911 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.72 (bs, 1H, NHCO), 5.85-5.78 (m, 2H, CH=CH), 3.87-3.83 (m, 1H, CH₂O), 3.69-

3.65 (dd, 1H, $J = 8.9, 11.8$, CH_2O), 3.54-3.50 (dd, 1H, $J = 4.6, 11.8$, CH_2O), 3.26-3.22 (m, 1H, OCH_2CH_2), 2.95-2.91 (m, 2H, OH, CH_3CH), 2.84 (d, 3H, $J = 5.2$, NHCH_3), 2.48-2.41 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 2.29-2.21 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 0.70 (d, 3H, $J = 6.8$, CH_3CHN). ^{13}C NMR (125.77 MHz, CDCl_3): δ 176.0, 129.5, 129.2, 79.4, 72.5, 69.9, 38.3, 36.3, 27.8, 25.9, 12.4; $[\alpha]_D^{23} = 16.3$ (c 1, CH_2Cl_2); MS (APCI): 214.1 ($\text{M}+1$, 100); HRMS (CI): m/z 213.1361 (213.1365 calc. for $\text{C}_{11}\text{H}_{19}\text{NO}_3$, M^+).

(2R,3S,6S,7R)-3,4,7-Trimethyl-2-phenyl-1,9-dioxo-4-azaspiro[5.7]tridec-11-en-5-one (20):

To a solution of the precursor diene (71mg, 0.21 mmol) in dichloromethane (40 ml) was added the Grubbs I catalyst (51 mg, 0.06 mmol, 30 mol %). The mixture was heated to reflux for 21 h and then the solvent was removed under pressure. The residue was purified by flash chromatography on silica gel to give 50 mg (77 %) of **20** as pale yellow oil.

IR (neat): 2940, 1636, 1452, 1380, 1146, 1132, 1037 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.60-7.47 (m, 5H, ArH), 5.83-5.75 (m, 2H, $\text{CH}=\text{CH}$), 5.47 (d, 1H, $J = 3.7$, PhCH), 4.68 (br d, 1H, $J = 17.4$, $\text{OCH}_2\text{CH}=\text{CH}$), 4.33 (dd, 1H, $J = 17.4, 1.8$, $\text{OCH}_2\text{CH}=\text{CH}$), 4.27 (t, 1H, $J = 11.8$, $\text{OCH}_2\text{CHCH}_3$), 3.75 (dq, 1H, $J = 6.9, 3.2$, NCHCH_3), 3.69 (dd, 1H, $J = 11.8, 3.7$, $\text{OCH}_2\text{CHCH}_3$), 3.42-3.38 (m, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.24 (s, 3H, NCH_3), 3.23-3.13 (m, 2H, CH_3CHCH_2 , $\text{CH}_2\text{CH}=\text{CH}_2$), 1.17 (d, 3H, $J = 9.8$, CH_3CHCH_2), 1.06 (d, 3H, $J = 6.9$, NCHCH_3); ^{13}C NMR (125.77 MHz, CDCl_3): δ 172.1, 138.6, 132.0, 128.5, 127.7, 125.7, 123.8, 82.2, 73.7, 71.4, 71.0, 59.1, 37.3, 33.8, 33.7, 13.3, 13.1; MS (APCI): 316.3 ($\text{M}+1$, 100); HRMS (CI): m/z 315.1830 (315.1834 calc. for $\text{C}_{19}\text{H}_{25}\text{NO}_3$, M^+).

(3R,4S,6S,7R)-4,6,7-Trihydroxy-N,3-dimethyloxocane-4-carboxamide (21):

To anhydrous liquid ammonia (distilled over sodium) was added Na (16 mg, 0.7 mmol) at -78°C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of the dihydroxylation product obtained from **20** (35 mg, 0.1 mmol) in anhydrous THF (2.5 ml) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3ml) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (3/2, ethyl acetate/hexane) to provide 8 mg (34%) of **21** as a colorless gum. This compound is very water-soluble.

IR (neat): 3375, 1646, 1540, 1458, 1412, 1264, 1145, 1093, 1055, 1019, 977 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.16 (br q, 1H, $J = 5$, NHCH_3), 5.47 (br s, 1H, OH), 4.7 (br m, 1H, CHOH), 3.96 (br dd, 1H, $J = 11$, 3, OCH_2), 3.8 (br s, 1H, CHOH), 3.68 (br t, 1H, $J = 11$, OCH_2), 3.60 (br d, 1H, $J = 12$, OCH_2), 3.39 (dd, 1H, $J = 12$, 4, OCH_2), 2.81 (d, 3H, $J = 5$, NHCH_3), 2.80 (m, 1H, CHCH_3), 2.53-2.48 (m, 1H, CCH_2CHOH), 2.02 (s, 1H, OH), 1.77 (br d, 1H, CCH_2CHOH), 0.65 (d, 3H, $J = 7$, CH_3CH); ^{13}C NMR (125.77 MHz, CDCl_3): δ 177.0, 78.3, 76.4, 72.9, 72.1, 70.5, 69.5, 29.9, 25.9, 11.4. $[\alpha]_D^{23} = -3.8$ (c 0.8, CH_2Cl_2); MS (APCI): 234.1 ($\text{M}+1$, 100); HRMS (CI): m/z 233.1259 (233.1263 calc. for $\text{C}_{10}\text{H}_{19}\text{NO}_5$, M^+).

Reference:

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