



Supporting Information

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Stereoselective Synthesis of Highly Substituted γ -Lactams From Acylsilanes

Robert B. Lettan II, Chase C. Woodward and Karl A. Scheidt*

Department of Chemistry, Northwestern University,
2145 Sheridan Road, Evanston, Illinois 60208

Supporting Information

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General Information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. THF was purified by passage through a bed of activated alumina.¹ Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.² Microwave reactions were carried out using a Biotage Initiator, SW version 1.2. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and/or ceric ammonium nitrate stain followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C-NMR spectra were recorded on a Varian Inova 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). Mass spectra data were obtained on a Varian 1200 Quadrupole Mass Spectrometer and Micromass Quadro II Spectrometer.

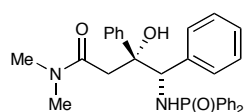
Benzoyltrimethylsilane was prepared according to the procedure of Yamamoto and coworkers.³ Diphenylphosphoryl imines were prepared from the corresponding oxime, according to the procedure of Boyd, Jennings, and coworkers.⁴

Representative procedure for the synthesis of γ -amino- β -hydroxy amides 1-8

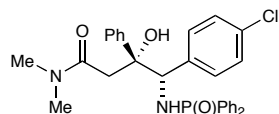
To a flame-dried, round-bottom flask equipped with a magnetic stirring bar and purged with nitrogen was added THF (2 mL) and diisopropylamine (0.54 mmol). The solution was cooled to -78 °C and *n*-butyllithium (1.6 M in hexanes, 0.54 mmol) was added by syringe. The reaction was warmed to 0 °C and stirred for 30 minutes. Dimethylacetamide (0.54 mmol) was added to the LDA solution and the reaction was stirred for one hour. The reaction was cooled to -78 °C, and a -78 °C solution of benzoyltrimethylsilane (0.59 mmol) in THF (0.5 mL) was added by cannula. The acylsilane delivery flask was rinsed with an additional portion of THF (0.5 mL), cooled to -78 °C and transferred to the reaction flask. The resulting homogeneous solution was stirred for 20 minutes after which a solution of the diphenylphosphoryl imine (0.65 mmol) in THF (2.0 mL) was added by cannula, again rinsing the delivery flask with an additional portion of THF (0.4 mL). The resulting reaction mixture was stirred at -78 °C for 15 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride (2 mL), warmed to ambient temperature, stirred for 30 minutes, and extracted with ethyl acetate (x3). The

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1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organomet.* **1996**, *15*, 1518-1520.
 2. Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd Ed., Pergamon Press, Oxford. 1988.
 3. Yamamoto, K.; Hayashi, A.; Suzuki, S.; Tsuji, J. *Organomet.* **1987**, *6*, 974-979.
 4. Boyd, D. R.; Malone, J. F.; McGuckin, M. R.; Jennings, W. B.; Rutherford, M.; Saket, B. M. *J. Chem. Soc., Perk. Trans. 2* **1988**, 1145-1150.

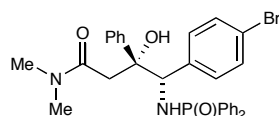
combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The unpurified silyl ether product was dissolved in THF (2 mL). To this solution was added tetrabutylammonium fluoride (1.0 M in THF, 1.1 mmol) and the mixture was stirred at room temperature for 30 minutes. The reaction was quenched by the addition of water, extracted with methylene chloride (x3), dried over anhydrous magnesium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.



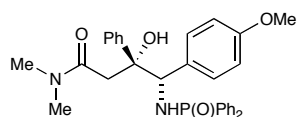
4-(diphenylphosphinamide)-3-hydroxy-*N,N*-dimethyl-3,4-diphenylbutanamide (1): Purified with 20-40% acetone/dichloromethane, yielding 192 mg (74%) of **1** as a white solid. R_f = 0.31 (30:70 acetone/dichloromethane); mp = 170 °C dec; IR (film) 3236, 3058, 2927, 1616, 1489, 1438, 1194, 1119, 721, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.85 (dd, 2H), 7.55-7.43 (m, 4H), 7.33 (t, 1H), 7.17-7.12 (m, 4H), 7.07-6.95 (m, 6H), 6.89 (s, 1H), 6.79 (d, 2H), 4.66 (t, 1H, J = 6.0 Hz), 4.24 (t, 1H, J = 6.5 Hz), 3.66 (d, 1H, J = 16.5 Hz), 3.36 (d, 1H, J = 16.5 Hz), 3.07 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.6, 144.2, 140.3, 133.2, 133.1, 131.6, 131.5, 128.9, 128.8, 128.7, 128.3, 128.1, 127.8, 127.2, 126.6(x2), 125.6, 78.7, 63.2, 40.4, 37.8, 35.4; LRMS (ESI): Mass calculated for $\text{C}_{30}\text{H}_{31}\text{N}_2\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$, 499.6. Found $[\text{M}+\text{H}]^+$, 499.7, $[\text{M}+\text{Na}]^+$, 521.6.



4-(diphenylphosphinamide)-4-(4-chlorophenyl)-3-hydroxy-*N,N*-dimethyl-3-phenylbutanamide (2): Purified with 20-40% acetone/dichloromethane, yielding 197 mg (71%) of **2** as a white solid. R_f = 0.33 (30:70 acetone/dichloromethane); mp = 165 °C dec; IR (film) 3231, 3057, 2959, 1621, 1487, 1438, 1196, 1119, 723, 699, 530 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.82 (dd, 2H), 7.53-7.42 (m, 5H), 7.34 (t, 1H), 7.19-6.90 (m, 9H), 6.72 (d, 2H), 4.64 (t, 1H, J = 11.0 Hz), 4.22 (t, 1H, J = 11.0 Hz), 3.99 (d, 1H, J = 11.0 Hz), 3.03 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.5, 143.9, 139.1, 133.1, 133.0, 132.3, 131.6, 131.5, 130.0, 128.9, 128.4, 128.2, 128.0, 127.4, 126.8, 125.5, 78.6, 62.5, 40.2, 37.8, 35.4; LRMS (ESI): Mass calculated for $\text{C}_{30}\text{H}_{30}\text{ClN}_2\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$, 534.0. Found $[\text{M}+\text{H}]^+$, 533.7.

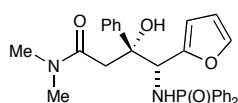


4-(diphenylphosphinamide)-4-(4-bromophenyl)-3-hydroxy-*N,N*-dimethyl-3-phenylbutanamide (3): Purified with 20-40% acetone/dichloromethane, yielding 211 mg (70%) of **3** as a white solid. R_f = 0.38 (30:70 acetone/dichloromethane); mp = 171 °C dec; IR (film) 3269, 3056, 2932, 1615, 1511, 1438, 1190, 1122, 725, 698, 521 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.80 (m, 2H), 7.53-7.32 (m, 6H), 7.18-6.96 (m, 9H), 6.67 (d, 2H), 4.65 (t, 1H, J = 11.0 Hz), 4.21 (t, 1H, J = 11.0 Hz), 3.58 (d, 1H, J = 16.5 Hz), 3.46 (s, 1H), 3.31 (d, 1H, J = 16.5 Hz), 3.01 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.5, 143.8, 139.6, 133.1, 132.3, 131.6, 131.5, 130.4, 130.3, 128.9, 128.8, 128.4, 128.3, 128.0, 126.9, 125.5, 120.6, 78.5, 62.6, 40.2, 37.8, 35.3 LRMS (ESI): Mass calculated for $\text{C}_{30}\text{H}_{30}\text{BrN}_2\text{O}_3\text{P}$ $[\text{M}]^+$, 577.5. Found $[\text{M}]^+$, 577.6.



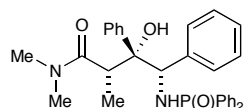
4-(diphenylphosphinamide)-3-hydroxy-4-(4-methoxyphenyl)-N,N-dimethyl-3-phenylbutanamide (4): Purified with 20-40% acetone/dichloromethane, yielding 195 mg (71%) of **4** as a white solid.

$R_f = 0.33$ (30:70 acetone/dichloromethane); mp = 175 °C dec; IR (film) 3231, 3056, 2929, 1616, 1495, 1435, 1192, 1119, 721, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.85-7.81 (m, 2H), 7.56-7.42 (m, 5H), 7.19-6.98 (m, 7H), 6.86 (s, 1H), 6.71 (m, 2H), 6.50 (m, 2H), 4.59 (t, 1H, $J = 11.0$ Hz), 4.22 (t, 1H, $J = 11.0$ Hz), 3.69 (s, 3H), 3.61 (d, 1H, $J = 16.5$ Hz), 3.33 (d, 1H, $J = 16.0$ Hz), 3.03 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.7, 158.2, 144.3, 133.2, 133.1, 132.1, 131.6, 131.5, 129.7, 128.9, 128.7, 128.3, 128.2, 127.8, 126.6, 125.6, 112.6, 78.8, 62.6, 55.2, 40.5, 37.8, 35.3; LRMS (ESI): Mass calculated for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_4\text{P}$ $[\text{M}+\text{H}]^+$, 529.6. Found $[\text{M}+\text{H}]^+$, 529.6.



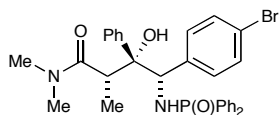
4-(diphenylphosphinamide)-4-(furan-3-yl)-3-hydroxy-N,N-dimethyl-3-phenylbutanamide (5): Purified with 20-40% acetone/dichloromethane, yielding 203 mg (80%) of **5** as a white solid. $R_f = 0.31$ (30:70

acetone/dichloromethane); mp = 180 °C dec; IR (film) 3254, 3057, 2932, 1617, 1489, 1438, 1200, 1119, 721, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.80 (m, 2H), 7.65-7.61 (m, 2H), 7.53-7.50 (m, 1H), 7.46-7.39 (m, 3H), 7.36-7.25 (m, 4H), 7.18-7.08 (m, 3H), 7.02 (bs, 1H), 5.97 (dd, 1H, $J = 2.0, 1.0$ Hz), 5.48 (d, 1H, $J = 3.0$ Hz), 4.51-4.48 (m, 2H), 3.53 (d, 1H, $J = 16.5$ Hz), 3.26 (d, 1H, $J = 16.0$ Hz), 3.00 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.6, 144.1, 137.9, 133.1, 133.0, 132.2, 132.1(x2), 132.0, 131.7, 131.6, 128.9, 128.8(x2), 128.7, 128.1, 127.9, 125.5, 78.9, 63.4, 40.5, 37.8, 35.4; LRMS (ESI): Mass calculated for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_4\text{P}$ $[\text{M}+\text{Na}]^+$, 511.5. Found $[\text{M}+\text{Na}]^+$, 511.6.



4-(diphenylphosphinamide)-3-hydroxy-N,N,2-trimethyl-3,4-diphenylbutanamide (6): Purified with 20-40% acetone/dichloromethane, yielding 224 mg (84%) of **6** as a white solid. $R_f = 0.40$ (30:70

acetone/dichloromethane); mp = 170 °C dec; IR (film) 3258, 3050, 2926, 1615, 1491, 1436, 1387, 1202, 1123, 727, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.83 (m, 2H), 7.57-7.41 (m, 5H), 7.30-7.28 (m, 2H), 7.16-6.89 (m, 8H), 6.74 (m, 2H), 6.38 (s, 1H), 4.68 (t, 1H, $J = 9.5$ Hz), 4.27 (t, 1H, $J = 10.0$ Hz), 3.53 (q, 1H, $J = 6.5$ Hz), 2.84 (s, 3H), 2.56 (s, 3H), 1.69 (d, 3H, $J = 6.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 177.3, 143.9, 141.0, 132.8, 132.7, 132.0, 131.9 (x2), 131.3, 128.9, 128.7, 128.6, 128.1, 128.0, 127.3, 126.9, 126.8, 79.5, 60.7, 42.3, 37.5, 35.3, 13.7; LRMS (ESI): Mass calculated for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$, 513.6. Found $[\text{M}+\text{H}]^+$, 513.5.

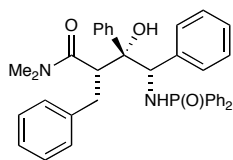


4-(diphenylphosphinamide)-4-(4-bromophenyl)-3-hydroxy-N,N,2-trimethyl-3-phenylbutanamide (7): Purified with 10-30%

acetone/dichloromethane, yielding 241 mg (78%) of **7** as a white solid.

R_f = 0.44 (30:70 acetone/dichloromethane); mp = 183-185 °C; IR (film)

3249, 3055, 2932, 1613, 1493, 1438, 1196, 1119, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.94-7.81 (m, 2H), 7.52-7.42 (m, 6H), 7.34-7.28 (m, 1H), 7.18-7.14 (m, 2H), 7.07-6.96 (m, 6H), 6.62 (d, 2H), 6.54 (s, 1H), 4.66 (t, 1H, J = 9.0 Hz), 3.40 (dd, 1H, J = 12.0, 9.0 Hz), 3.53 (q, 1H, J = 7.0 Hz), 2.84 (s, 3H), 2.57 (s, 3H), 1.71 (d, 3H, J = 7.0 Hz); ^{13}C NMR (400 MHz, CDCl_3) δ 177.2, 143.9, 140.4, 132.6, 132.5, 132.1, 131.8, 131.7, 131.4, 130.6, 130.3, 128.8, 128.7, 128.1, 128.0, 127.0, 120.6, 79.3, 60.2, 42.7, 37.5, 35.3, 13.9; LRMS (ESI): Mass calculated for $\text{C}_{31}\text{H}_{32}\text{BrN}_2\text{O}_3\text{P}$ $[\text{M}]^+$, 591.5. Found $[\text{M}]^+$, 591.7.



4-(diphenylphosphinamide)-2-benzyl-3-hydroxy-N,N-dimethyl-3,4-diphenylbutanamide (8): Purified with 5-10% acetone/dichloromethane,

yielding 231 mg (75%) of **8** as a white solid. R_f = 0.73 (30:70

acetone/dichloromethane); mp = 175 °C dec; IR (film) 3273, 2926, 2856,

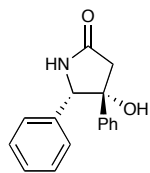
1698, 1493, 1412, 1205, 1090, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.83-

7.79 (m, 2H), 7.57-7.53 (m, 2H), 7.46-7.09 (m, 13H), 7.01-6.91 (m, 6H), 6.85 (d, 2H), 6.59 (s, 1H), 4.89 (t, 1H, J = 9.5 Hz), 4.34 (t, 1H, J = 10.5 Hz), 4.21 (dd, 1H J = 12.0, 3.5 Hz), 3.67 (dd, 1H, J = 11.0, 3.5 Hz), 3.28 (d, 1H, J = 12.5 Hz), 2.25 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 175.3, 143.9, 141.4, 139.6, 132.9, 132.8, 132.0, 131.8, 131.7, 131.4, 129.8, 129.0, 128.8, 128.7, 128.4, 128.1, 127.9, 127.4, 126.9, 126.8, 126.7, 79.9, 61.1, 51.2, 36.7, 34.8, 34.7; LRMS (ESI): Mass calculated for $\text{C}_{37}\text{H}_{37}\text{N}_2\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$, 589.7. Found $[\text{M}+\text{H}]^+$, 589.7.

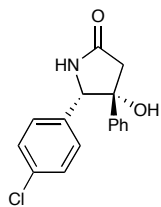
Representative procedure for the preparation of β -hydroxy- γ -lactams 9-16

Condition A: A 0.5-2.0 mL Biotage microwave flask equipped with a stirbar was charged with the γ -amino- β -hydroxy amide (0.20 mmol), tetrahydrofuran (1.0 mL), and 3 M aqueous HCl (1.0 mL). The resulting mixture was stirred for 2 minutes, heated to 150 °C in the microwave, and stirred at this temperature for an additional 5 minutes. The resulting mixture was cooled to ambient temperature, slowly neutralized with solid sodium bicarbonate (evolution of gas ceases) and extracted with dichloromethane (x3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

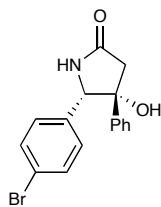
Condition B: A 0.5-2.0 mL Biotage microwave flask equipped with a stirbar was charged with the γ -amino- β -hydroxy amide (0.20 mmol), tetrahydrofuran (1.0 mL), and 3 M aqueous HCl (1.0 mL). The resulting mixture was stirred for 2 minutes, heated to 70 °C in the microwave, and stirred at this temperature for an additional 10 minutes. The resulting mixture was cooled to ambient temperature, slowly neutralized with solid sodium bicarbonate (evolution of gas ceases) and extracted with dichloromethane (x3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.



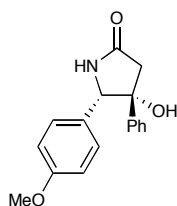
4-hydroxy-4,5-diphenylpyrrolidin-2-one (9): Purified with 10-30% acetone/dichloromethane, yielding 50 mg (98%) of **9** as a white solid. $R_f = 0.19$ (20:80 acetone/dichloromethane); mp = 198-200 °C; IR (film) 3303, 3188, 1701, 1668, 1443, 1337, 1214, 1071, 1031, 732, 691 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.35 (m, 8H), 7.10 (d, 2H), 6.07 (s, 1H), 5.19 (s, 1H), 3.06 (d, 1H, $J = 21.5$ Hz), 2.83 (d, 1H, $J = 21.5$ Hz), 1.78 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.5, 142.5, 133.7, 129.4, 128.8, 128.0, 127.4, 125.4, 79.6, 69.4, 47.6; LRMS (ESI): Mass calculated for $\text{C}_{16}\text{H}_{15}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 254.3. Found $[\text{M}+\text{H}]^+$, 254.5.



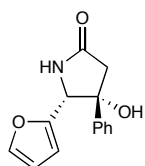
5-(4-chlorophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (10): Purified with 20-40% acetone/dichloromethane, yielding 56 mg (97%) of **10** as a white solid. $R_f = 0.42$ (30:70 acetone/dichloromethane); mp = 173-175 °C; IR (film) 3283, 2924, 1693, 1489, 1409, 1332, 1204, 1065, 1011, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.41-7.29 (m, 7H), 7.02 (d, 2H), 6.48 (s, 1H), 5.13 (s, 1H), 3.08 (d, 1H, $J = 17.5$ Hz), 2.81 (d, 1H, $J = 17.0$ Hz), 1.95 (bs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.7, 142.1, 135.1, 132.4, 129.2, 128.9 (x2), 128.2, 125.4, 79.7, 69.0, 47.6; LRMS (ESI): Mass calculated for $\text{C}_{16}\text{H}_{14}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$, 288.7. Found $[\text{M}+\text{H}]^+$, 288.4.



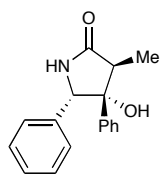
5-(4-bromophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (11): Purified with 20-40% acetone/dichloromethane, yielding 62 mg (93%) of **11** as a white solid. $R_f = 0.40$ (30:70 acetone/dichloromethane); mp = 144-146 °C; IR (film) 3283, 2924, 1693, 1489, 1409, 1332, 1204, 1065, 1011, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.45-7.34 (m, 7H), 6.95 (d, 2H), 6.78 (s, 1H), 5.10 (s, 1H), 3.07 (d, 1H, $J = 17.0$ Hz), 2.79 (d, 1H, $J = 17.5$ Hz), 1.55 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.6, 142.0, 132.9, 132.2, 129.2, 128.9, 128.2, 125.4, 123.3, 79.6, 69.0, 47.6 LRMS (ESI): Mass calculated for $\text{C}_{16}\text{H}_{14}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$, 333.2. Found $[\text{M}+\text{H}]^+$, 333.0.



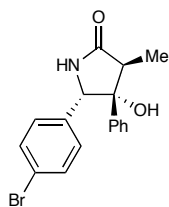
4-hydroxy-5-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (12): Purified with 10-30% acetone/dichloromethane, yielding 53 mg (94%) of **12** as a white solid. $R_f = 0.21$ (20:80 acetone/dichloromethane); mp = 169-171 °C; IR (film) 3323, 2927, 2833, 1697, 1611, 1517, 1423, 1251, 1178, 1034, 732, 704 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.28 (m, 2H), 6.99 (d, 2H), 6.84 (d, 2H), 6.74 (s, 1H), 5.13 (s, 1H), 3.78 (s, 3H), 3.03 (d, 1H, $J = 17.0$ Hz), 2.80 (d, 1H, $J = 17.0$ Hz), 1.99 (bs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.1, 160.3, 142.7, 128.7 (x2), 127.9, 125.5, 125.3, 114.5, 79.5, 69.2, 55.5, 47.6; LRMS (ESI): Mass calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$, 284.3. Found $[\text{M}+\text{H}]^+$, 284.5.



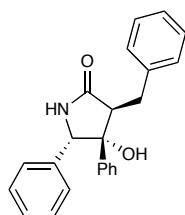
5-(furan-3-yl)-4-hydroxy-4-phenylpyrrolidin-2-one (13): Purified with 10-30% acetone/dichloromethane, yielding 47 mg (97%) of **13** as a white solid. $R_f = 0.28$ (20:80 acetone/dichloromethane); mp = 206-208 °C; IR (film) 3291, 3054, 2919, 1697, 1509, 1447, 1312, 1206, 1060, 810, 703 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.72 (m, 3H), 7.53-7.51 (m, 1H), 7.46-7.35 (m, 3H), 7.01 (d, 1H), 6.08 (s, 1H), 5.35 (s, 1H), 3.11 (d, 1H, $J = 17.5$ Hz), 2.88 (d, 1H, $J = 17.5$ Hz), 1.82 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.5, 142.6, 133.2, 128.8, 128.1, 128.0, 127.0, 125.4, 79.7, 69.6, 47.6; LRMS (ESI): Mass calculated for $\text{C}_{14}\text{H}_{13}\text{NO}_3$ $[\text{M}+\text{H}]^+$, 244.3. Found $[\text{M}+\text{H}]^+$, 244.4.



4-hydroxy-3-methyl-4,5-diphenylpyrrolidin-2-one (14): Purified with 10-30% acetone/dichloromethane, yielding 51 mg (96%) of **14** as a white solid. $R_f = 0.55$ (30:70 acetone/dichloromethane); mp = 144-146 °C; IR (film) 3263, 3060, 2926, 1699, 1491, 1446, 1337, 1119, 1019, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.59-7.57 (d, 2H), 7.42-7.31 (m, 8H), 6.46 (s, 1H), 5.37 (s, 1H), 2.70 (q, 1H, $J = 7.5$ Hz), 1.85 (s, 1H), 0.91 (d, 3H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 178.8, 141.1, 135.2, 129.3, 129.2, 128.7, 128.2, 128.0, 126.3, 100.0, 82.2, 64.6, 49.6, 12.9; LRMS (ESI): Mass calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 268.3. Found $[\text{M}+\text{H}]^+$, 268.6.



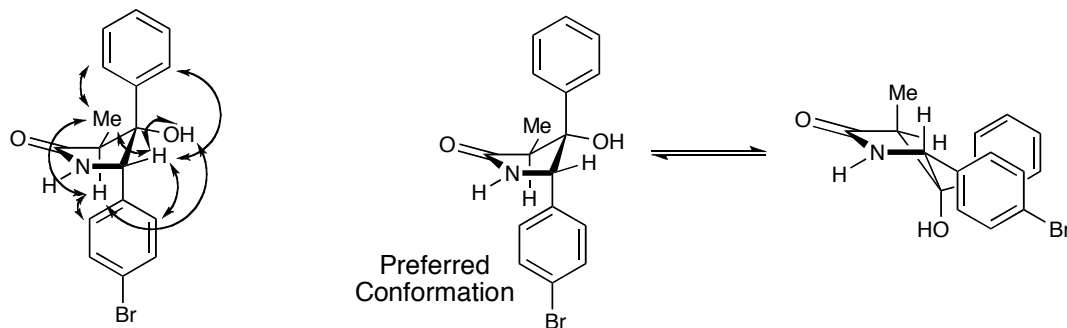
5-(4-bromophenyl)-4-hydroxy-3-methyl-4-phenylpyrrolidin-2-one (15): Purified with 2-30% acetone/dichloromethane, yielding 68 mg (98%) of **15** as a white solid. $R_f = 0.29$ (10:90 acetone/dichloromethane); mp = 181-183 °C; IR (film) 3344, 2919, 1701, 1492, 1456, 1071, 1014, 761, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.56 (d, 2H), 7.47-7.33 (m, 5H), 7.18 (d, 2H), 6.99 (s, 1H), 5.34 (s, 1H), 2.66 (q, 1H, $J = 7.5$ Hz), 1.85 (s, 1H), 0.89 (d, 3H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 178.9, 140.6, 134.2, 132.3, 129.6, 128.8, 128.4, 126.2, 125.7, 82.2, 64.1, 49.6, 30.5; LRMS (ESI): Mass calculated for $\text{C}_{17}\text{H}_{16}\text{BrNO}_2$ $[\text{M}]^+$, 346.2. Found $[\text{M}]^+$, 346.4.



3-benzyl-4-hydroxy-4,5-diphenylpyrrolidin-2-one (16): Purified with 5-20% acetone/dichloromethane, yielding 62 mg (90%) of **16** as a white solid. $R_f = 0.51$ (10:90 acetone/dichloromethane); mp = 56-58 °C; IR (film) 3270, 3029, 2915, 1693, 1492, 1451, 1333, 1063, 907, 728, 695 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.55 (d, 2H), 7.42-7.29 (m, 7H), 7.19-7.08 (m, 3H), 7.00 (s, 1H), 6.91 (d, 2H), 6.44 (s, 1H), 5.06 (s, 1H), 3.07 (dd, 1H, $J = 8.0, 6.0$ Hz), 2.97 (dd, 1H, $J = 15.0, 6.0$ Hz), 2.51 (dd, 1H, $J = 15.0, 8.0$ Hz), 1.61 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 177.3, 142.4, 139.2, 136.0, 129.2, 129.1, 128.8, 128.4, 128.3, 128.0, 126.3, 126.0, 81.7, 66.2, 54.6, 32.6; LRMS (ESI): Mass calculated for $\text{C}_{23}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$, 344.4. Found $[\text{M}+\text{H}]^+$, 344.6.

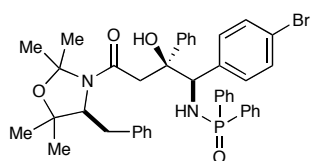
Stereochemical determination of β -hydroxy amide **14**

The relative stereochemistry of β -hydroxy amide **14** was determined by ^1H NOE spectroscopy. See NMR spectra, pages 23-25.



Procedure for the synthesis of γ -amino- β -hydroxy amide **18**

To a flame-dried, round-bottom flask equipped with a magnetic stir bar and purged with nitrogen was added THF (2.0 mL) and diisopropylamine (0.62 mmol). The resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-butyllithium (1.6 M in hexanes, 0.62 mmol) was added dropwise by syringe. The reaction was warmed to $0\text{ }^{\circ}\text{C}$, stirred for 30 minutes, then cooled to $-78\text{ }^{\circ}\text{C}$. To this solution of LDA was added a $-78\text{ }^{\circ}\text{C}$ solution of chiral amide **17** (0.62 mmol) in THF (0.7 mL + 0.3 mL rinse) by cannulation. The resulting reaction was warmed to $0\text{ }^{\circ}\text{C}$, stirred for 1 hour, then recooled to $-78\text{ }^{\circ}\text{C}$. To the reaction was added a cooled to $-78\text{ }^{\circ}\text{C}$ solution of benzoyltrimethylsilane (0.56 mmol) in THF (0.7 mL) in one portion by cannula, again rinsing the delivery flask with an additional portion of THF (0.3 mL). The resulting reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 minutes, monitoring for consumption of benzoyltrimethylsilane by TLC ($R_f = 0.67$ (10:90 ethyl acetate/hexanes)). Following consumption of benzoyltrimethylsilane, the reaction was warmed to $0\text{ }^{\circ}\text{C}$, stirred for 30 minutes, and recooled to $-78\text{ }^{\circ}\text{C}$. *This equilibration period at $0\text{ }^{\circ}\text{C}$ is necessary for the increased diastereoselectivity.* A solution of the *N*-phosphinoyl imine (0.67 mmol) in THF (1.3 mL) was added in one portion by cannula, again rinsing the delivery flask with an additional portion of THF (0.3 mL). Following addition of the imine, the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride (2 mL), warmed to ambient temperature, stirred for 30 minutes, and extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The unpurified silyl ether product was dissolved in THF (2 mL) and tetrabutylammonium fluoride (1.0 M in THF, 0.84 mmol) was added. After 30 min, the desilylation reaction was quenched by the addition of water, extracted with methylene chloride (x3), dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.



***N*-((1*R*,2*S*)-4-((*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidin-3-yl)-1-(4-bromophenyl)-2-hydroxy-4-oxo-2-phenylbutyl)-*P,P*-diphenylphosphinic amide (**18**):** Purified with 5-20% acetone/dichloromethane, yielding 286 mg (68%) of **18** as a pale yellow solid. $R_f = 0.41$ (10:90 acetone/dichloromethane); mp = 99-

102 $^{\circ}\text{C}$; IR (film) 3273, 2978, 1607, 1436, 1415, 1201, 1123, 1010, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.74 (m, 2H), 7.56-7.28 (m, 10H), 7.25-6.91 (m, 10H), 6.66 (d, 2H), 6.60 (s, 1H), 4.29-4.26 (m, 2H), 3.87 (t, 1H, $J = 7.0$ Hz), 2.98 (dd, 1H, $J = 6.0, 14.0$ Hz), 2.85-2.62 (m, 2H), 2.31 (d, 1H, $J = 15.0$ Hz), 1.63 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 143.5, 139.4, 137.4, 132.7, 132.6, 131.8, 131.7, 130.7, 130.3, 130.2, 129.5, 128.9, 128.8, 128.2, 128.1 (x2), 127.2, 127.1, 120.6, 94.8, 80.6, 79.0 (x2), 67.2, 61.8, 42.9, 39.0, 31.2, 28.7, 17.5; LRMS (ESI): Mass calculated for $\text{C}_{42}\text{H}_{44}\text{BrN}_2\text{O}_4\text{P}$ $[\text{M}+\text{H}]^+$, 751.2. Found $[\text{M}+\text{H}]^+$, 751.2.

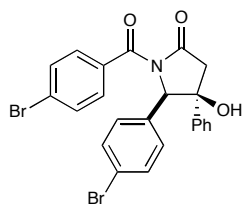
Procedure for the synthesis of β -hydroxy lactam **19**

γ -Amino- β -hydroxy amide **18** (0.38 mmol) was transferred to a 2.0-5.0 mL Biotage microwave flask equipped with a stirbar. The solid was dissolved in THF (1.5 mL) and 3M aqueous HCl (3.0 mL). The reaction mixture was stirred for 2 minutes, heated to 150 °C in the microwave, and stirred at this temperature for 20 minutes. The resulting mixture was cooled to ambient temperature and slowly neutralized with solid sodium bicarbonate (evolution of gas ceases) and extracted with dichloromethane (x3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel (2-30% acetone/dichloromethane), yielding 77 mg (63%) of **(4S,5R)-5-(4-bromophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (19)** as a white solid. ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, and melting point data are equivalent to that observed for β -hydroxy lactam **11**. Chiral HPLC analysis (see page 10) indicates an 87% ee, corresponding to approximately a 14:1 diastereoselectivity in relation to the chiral auxiliary for the addition event. β -Hydroxy lactam **19** was also recovered without purification and isolation of γ -amino- β -hydroxy amide **18** (63% yield overall, 87% ee). This experiment was conducted to insure that the observed selectivity was not being unintentionally augmented during intermediate **18** purification.

Determination of the absolute stereochemistry of β -hydroxy lactam **19**

The absolute configuration of β -hydroxy lactam **19** was determined by single crystal X-ray diffraction of **(4S,5R)-5-(4-bromophenyl)-1-(4-bromophenylcarbonyl)-4-hydroxy-4-phenylpyrrolidin-2-one (20)**, which was prepared from **19** as follows:

To a round-bottom flask equipped with a magnetic stir bar and purged with nitrogen was dissolved lactam **19** (0.069 mmol) in THF (350 μL), and cooled in an ice-water bath. To the cooled solution was added NaH (0.152 mmol, 60% in mineral oil) in one portion, and stirred at 0 °C for 15 minutes. To the reaction was added 4-bromobenzoyl chloride in one portion, and stirred at 0 °C for 5 hours. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl , extracted with CH_2Cl_2 (x3), dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by flash column chromatography on silica gel.



(4S,5R)-5-(4-bromophenyl)-1-(4-bromophenylcarbonyl)-4-hydroxy-4-phenylpyrrolidin-2-one (20): Purified with 80% dichloromethane/hexanes, yielding 21 mg (59%) of **20** as a pale yellow solid. R_f = 0.41 (80:20 dichloromethane/hexanes); mp = 268-271 °C; IR (film) 2919, 1748, 1689, 1658, 1587, 1484, 1447, 1273, 1232, 1176, 1070, 1032, 1010, 963, 896, 841, 806, 779, 765, 745, 715, 701, 597 cm^{-1} ; ^1H

NMR (500 MHz, CDCl_3) δ 7.74-7.73 (m, 2H), 7.63-7.61 (m, 2H), 7.44-7.38 (m, 7H), 6.92-6.90 (m, 2H), 5.69 (s, 1H), 3.21 (d, 1H, J = 18.5 Hz), 3.06 (d, 1H, J = 18.0 Hz), 1.41 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.7, 170.0, 140.9, 132.8, 132.3, 131.9 (x2), 131.8, 129.1, 128.8, 128.7, 128.6, 125.3, 123.2, 76.0, 71.6, 48.6; LRMS (ESI): Molecular weight calculated for $\text{C}_{23}\text{H}_{17}\text{Br}_2\text{NO}_3$ $[\text{M}+\text{H}]^+$, 516.2. Mass found $[\text{M}+\text{H}]^+$, 516.1.

HPLC analysis of γ -amino- β -hydroxy lactams 11 and 19 **γ -amino- β -hydroxy lactam 22**

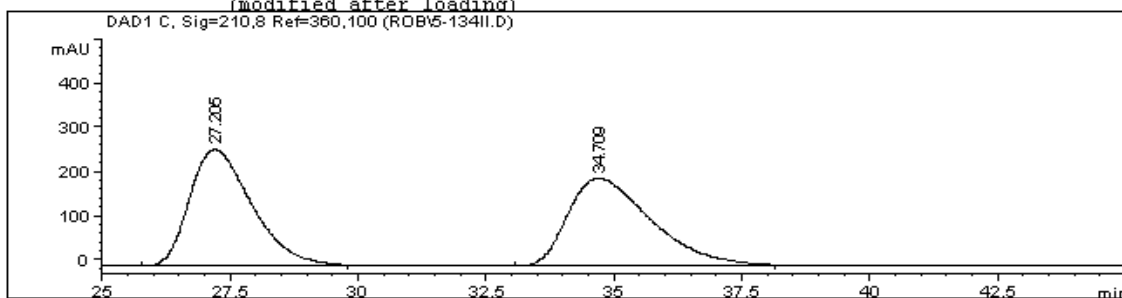
HPLC conditions: 90:10 hexanes:isopropanol, 1.0 mL/min, OD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\ROB\5-134II.D

Sample Name: RBL5-134II

Ad-H column, 10%IPA/hex

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=====
Injection Date   : 4/27/2007 11:29:10 AM
Sample Name      : RBL5-134II                Location : Vial 41
Acq. Operator    : rob                      Inj Volume : 5  $\mu$ l
Acq. Method      : C:\HPCHEM\2\METHODS\ROB.M
Last changed     : 4/27/2007 11:26:27 AM by rob
                  (modified after loading)
Analysis Method  : C:\HPCHEM\2\METHODS\SCHWIN1.M
Last changed     : 5/17/2007 4:16:02 PM by ROB
                  (modified after loading)
DAD1 C, Sig=210,8 Ref=360,100 (ROB\5-134II.D)
```



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=====
                          Area Percent Report
=====
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
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Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.205	BB	1.2366	2.21196e4	262.64490	50.0340
2	34.709	BB	1.5671	2.20895e4	197.46222	49.9660

Totals : 4.42091e4 460.10712

Results obtained with enhanced integrator!

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*** End of Report ***
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Optically active γ -amino- β -hydroxy lactam **19:**

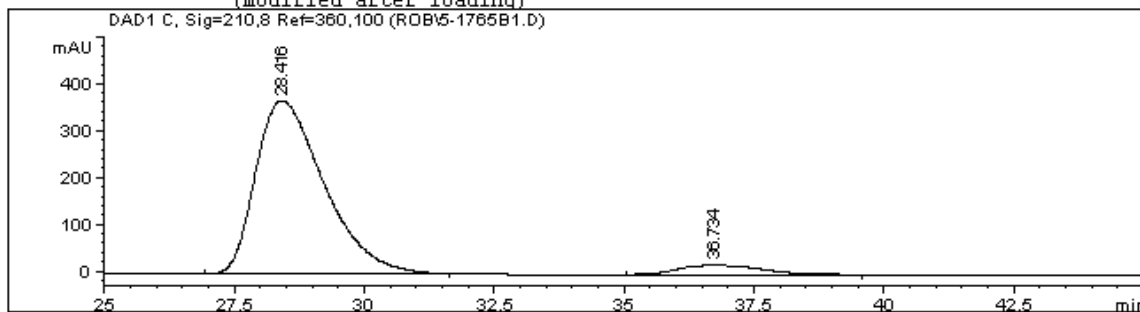
HPLC conditions: 90:10 hexanes:isopropanol, 1.0 mL/min, OD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\ROB\5-1765B1.D

Sample Name: RBL5-176VB

ODH, 10% IPA/Hex

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Injection Date   : 5/17/2007 1:02:04 AM
Sample Name      : RBL5-176VB           Location : Vial 41
Acq. Operator    : ROB                  Inj Volume : 5  $\mu$ l
Acq. Method      : C:\HPCHEM\2\METHODS\ROB.M
Last changed     : 5/16/2007 10:21:17 PM by ROB
                  (modified after loading)
Analysis Method  : C:\HPCHEM\2\METHODS\SCHWIN1.M
Last changed     : 5/17/2007 4:14:10 PM by ROB
                  (modified after loading)
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=====
                          Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.416	BB	1.3506	3.38655e4	369.74170	93.2112
2	36.734	BB	1.3602	2466.50146	21.37524	6.7888

Totals : 3.63320e4 391.11694

Results obtained with enhanced integrator!

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*** End of Report ***
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Stereochemical determination of β -hydroxy amide **11**

The relative stereochemistry of **11** was determined by X-ray crystallography. Amide **11** was crystallized by slow diffusion of hexanes into methylene chloride.

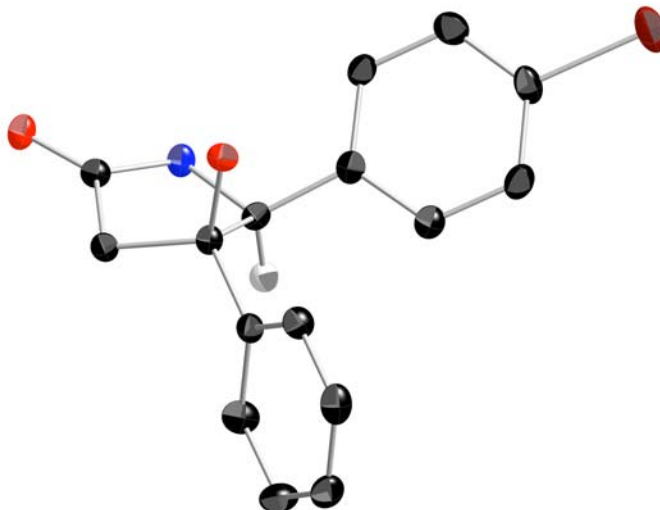


Table 1. Crystal data and structure refinement for **11**.

Identification code	s59vm
Empirical formula	C ₁₇ H ₁₄ BrCl ₂ NO ₂ (+ CH ₂ Cl ₂)
Formula weight	417.11
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system, space group	triclinic, P-1
Unit cell dimensions	a = 7.4375(5) Å; α = 93.6070(10) ° b = 8.8670(6) Å; β = 97.4310(10) ° c = 14.4876(10) Å; γ = 113.7950(10) °
Volume	859.87(10) Å ³
Z, Calculated density	2, 1.466 Mg/m ³
Absorption coefficient	2.551 mm ⁻¹
F(000)	382
Crystal size	0.36 x 0.24 x 0.10 mm
Theta range for data collection	1.43 to 28.48 °
Limiting indices	-9 ≤ h ≤ 9, -11 ≤ k ≤ 11, -19 ≤ l ≤ 18
Reflections collected / unique	7903 / 3902 [R(int) = 0.0750]
Completeness to theta = 28.48	90.1 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3902 / 0 / 216
Goodness-of-fit on F ²	0.974
Final R indices [I > 2sigma(I)]	R1 = 0.0354, wR2 = 0.0916
R indices (all data)	R1 = 0.0433, wR2 = 0.0970
Largest diff. peak and hole	0.932 and -0.509 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **11**.

	x	y	z	U(eq)
Br	11981(1)	3014(1)	10586(1)	39(1)
C(1)	8108(3)	1120(2)	4964(1)	17(1)
C(2)	6840(3)	2092(2)	5018(1)	16(1)
C(3)	7220(3)	2691(2)	6072(1)	15(1)
C(4)	9456(3)	2986(2)	6351(1)	15(1)
C(5)	6849(3)	4221(2)	6312(1)	17(1)
C(6)	7739(3)	5656(2)	5890(2)	23(1)
C(7)	7437(3)	7067(3)	6115(2)	27(1)
C(8)	6226(3)	7073(3)	6771(2)	25(1)
C(9)	5321(3)	5657(3)	7186(2)	24(1)
C(10)	5634(3)	4243(2)	6964(2)	20(1)
C(11)	10075(3)	2933(2)	7375(1)	18(1)
C(12)	10272(3)	1561(2)	7713(2)	21(1)
C(13)	10826(3)	1574(3)	8670(2)	25(1)
C(14)	11184(3)	2962(3)	9279(2)	24(1)
C(15)	11010(3)	4347(3)	8965(2)	24(1)
C(16)	10447(3)	4314(2)	8007(2)	21(1)
C(17)	5645(4)	207(3)	8601(2)	35(1)
Cl(1)	3211(1)	-1150(1)	8036(1)	46(1)
Cl(2)	5648(1)	1895(1)	9307(1)	44(1)
N(1)	9564(2)	1695(2)	5707(1)	18(1)
O(1)	7834(2)	-7(2)	4339(1)	19(1)
O(2)	6128(2)	1344(2)	6542(1)	17(1)

Table 3. Bond lengths [$\text{\AA}$] for **11**.

Br-C(14)	1.901(2)
C(1)-O(1)	1.238(2)
C(1)-N(1)	1.333(2)
C(1)-C(2)	1.518(3)
C(2)-C(3)	1.535(3)
C(3)-O(2)	1.419(2)
C(3)-C(5)	1.518(3)
C(3)-C(4)	1.569(2)
C(4)-N(1)	1.465(2)
C(4)-C(11)	1.505(3)
C(5)-C(10)	1.393(3)
C(5)-C(6)	1.398(3)
C(6)-C(7)	1.385(3)
C(7)-C(8)	1.391(3)
C(8)-C(9)	1.382(3)
C(9)-C(10)	1.391(3)
C(11)-C(16)	1.391(3)

C(11)-C(12)	1.393(3)
C(12)-C(13)	1.393(3)
C(13)-C(14)	1.379(3)
C(14)-C(15)	1.384(3)
C(15)-C(16)	1.391(3)
C(17)-Cl(2)	1.758(3)
C(17)-Cl(1)	1.770(3)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **11**.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br	55(1)	55(1)	18(1)	0(1)	-1(1)	37(1)
C(1)	15(1)	19(1)	18(1)	3(1)	6(1)	8(1)
C(2)	16(1)	19(1)	16(1)	2(1)	3(1)	10(1)
C(3)	13(1)	18(1)	16(1)	1(1)	3(1)	8(1)
C(4)	13(1)	16(1)	19(1)	1(1)	4(1)	8(1)
C(5)	16(1)	20(1)	16(1)	1(1)	1(1)	9(1)
C(6)	26(1)	24(1)	26(1)	6(1)	13(1)	14(1)
C(7)	32(1)	21(1)	31(1)	7(1)	10(1)	4(1)
C(8)	28(1)	26(1)	26(1)	-2(1)	2(1)	19(1)
C(9)	22(1)	33(1)	22(1)	-3(1)	4(1)	17(1)
C(10)	20(1)	24(1)	20(1)	3(1)	5(1)	10(1)
C(11)	11(1)	21(1)	20(1)	0(1)	2(1)	7(1)
C(12)	21(1)	21(1)	20(1)	-3(1)	1(1)	11(1)
C(13)	26(1)	28(1)	25(1)	5(1)	3(1)	16(1)
C(14)	22(1)	37(1)	16(1)	-3(1)	-2(1)	16(1)
C(15)	26(1)	26(1)	22(1)	-4(1)	3(1)	13(1)
C(16)	20(1)	22(1)	22(1)	0(1)	3(1)	9(1)
C(17)	32(1)	51(1)	32(1)	13(1)	13(1)	26(1)
Cl(1)	40(1)	36(1)	62(1)	-7(1)	16(1)	13(1)
Cl(2)	35(1)	47(1)	44(1)	-5(1)	3(1)	13(1)
N(1)	15(1)	23(1)	18(1)	-1(1)	2(1)	12(1)
O(1)	18(1)	22(1)	19(1)	-4(1)	2(1)	10(1)
O(2)	14(1)	18(1)	21(1)	4(1)	3(1)	7(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **11**.

	x	y	z	U(eq)
H(2A)	5412	1373	4790	19
H(2B)	7273	3041	4649	19
H(4)	10320(30)	4100(30)	6185(17)	19
H(6)	8565	5663	5440	28
H(7)	8056	8032	5822	32
H(8)	6024	8042	6931	30
H(9)	4478	5650	7627	29
H(10)	5012	3282	7259	25
H(12)	10029	612	7288	25

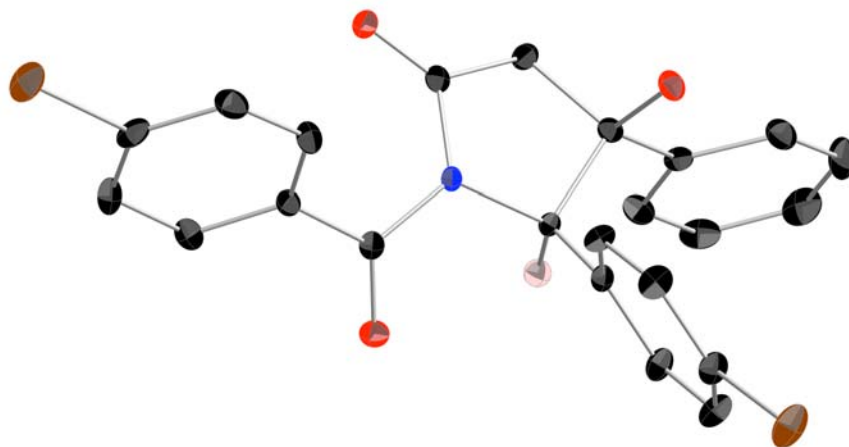
H(13)	10955	637	8901	30
H(15)	11269	5297	9392	29
H(16)	10315	5253	7781	25
H(17A)	6219	-416	8995	41
H(17B)	6498	630	8121	41
H(1)	10450(40)	1380(30)	5760(19)	28(7)
H(2)	4907	989	6326	26

Table 6. Torsion angles (°) for **11**.

O(1)-C(1)-N(1)	126.18(18)
O(1)-C(1)-C(2)	125.96(17)
N(1)-C(1)-C(2)	107.86(16)
C(1)-C(2)-C(3)	102.74(15)
O(2)-C(3)-C(5)	112.35(16)
O(2)-C(3)-C(2)	109.10(14)
C(5)-C(3)-C(2)	114.85(16)
O(2)-C(3)-C(4)	105.22(14)
C(5)-C(3)-C(4)	113.39(15)
C(2)-C(3)-C(4)	100.96(15)
N(1)-C(4)-C(11)	115.08(15)
N(1)-C(4)-C(3)	101.50(14)
C(11)-C(4)-C(3)	114.26(16)
C(10)-C(5)-C(6)	118.16(18)
C(10)-C(5)-C(3)	121.20(18)
C(6)-C(5)-C(3)	120.64(18)
C(7)-C(6)-C(5)	121.1(2)
C(6)-C(7)-C(8)	120.0(2)
C(9)-C(8)-C(7)	119.40(19)
C(8)-C(9)-C(10)	120.6(2)
C(9)-C(10)-C(5)	120.7(2)
C(16)-C(11)-C(12)	119.06(19)
C(16)-C(11)-C(4)	118.13(17)
C(12)-C(11)-C(4)	122.80(18)
C(13)-C(12)-C(11)	120.29(19)
C(14)-C(13)-C(12)	119.27(19)
C(13)-C(14)-C(15)	121.8(2)
C(13)-C(14)-Br	119.82(16)
C(15)-C(14)-Br	118.39(16)
C(14)-C(15)-C(16)	118.35(19)
C(11)-C(16)-C(15)	121.25(19)
Cl(2)-C(17)-Cl(1)	111.78(13)
C(1)-N(1)-C(4)	113.86(16)

Stereochemical determination of β -hydroxy amide 19

The absolute stereochemistry of **19** was determined by X-ray crystallography of **20**. Amide **20** was crystallized by slow diffusion of hexanes into methylene chloride.

Table 1. Crystal data and structure refinement for **20**.

Identification code	s23w_1_0m
Empirical formula	C ₂₃ H ₁₇ Br ₂ NO ₃
Formula weight	515.20
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, P21
Unit cell dimensions	a = 14.0078(3) Å; α = 90.00 ° b = 5.54060(10) Å; β = 117.0080(10) ° c = 14.8626(3) Å; γ = 90.00 °
Volume	102.71(4) Å ³
Z, Calculated density	2, 1.665 Mg/m ³
Absorption coefficient	3.968 mm ⁻¹
F(000)	512
Crystal size	0.509 x 0.108 x 0.020 mm
Theta range for data collection	1.54 to 30.33 °
Limiting indices	-19≤h≤19, -7≤k≤7, -20≤l≤21
Reflections collected / unique	5027 / 4166 [R(int) = 0.0596]
Completeness to theta = 30.33	90.1 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5027 / 1 / 266
Goodness-of-fit on F ²	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0712
R indices (all data)	R1 = 0.0437, wR2 = 0.1045
Largest diff. peak and hole	3.593 (max) and 0.028 (min) Å ⁻³

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$) for **20**.

	x	y	z	U(eq)
O(1)	0.4215(2)	-0.0724(5)	0.9126(2)	0.0151(6)
Br(1)	0.67975(3)	0.05678(10)	0.47016(3)	0.02517(13)
Br(2)	-0.03876(3)	0.10801(8)	0.59249(3)	0.02565(13)
O(3)	0.4757(2)	0.5253(5)	0.7831(2)	0.0152(6)
C(7)	0.2557(3)	0.4433(8)	0.7486(3)	0.0159(9)
C(11)	0.2877(3)	0.0539(8)	0.6952(3)	0.0165(8)
C(22)	0.9274(4)	0.2864(8)	1.1345(3)	0.0207(10)
C(15)	0.6627(3)	0.1022(8)	0.5890(3)	0.0168(8)
C(23)	0.8234(3)	0.2286(8)	1.0656(3)	0.0174(9)
C(5)	0.4423(3)	0.3278(7)	0.7904(3)	0.0127(8)
O(2)	0.6898(2)	-0.2566(5)	0.8808(2)	0.0160(6)
C(1)	0.5046(3)	-0.0168(7)	0.9107(3)	0.0121(8)
C(2)	0.6277(3)	0.1661(7)	0.8588(3)	0.0116(8)
C(6)	0.3268(3)	0.2710(7)	0.7460(3)	0.0123(8)
C(3)	0.6871(3)	-0.0459(7)	0.9334(3)	0.0117(8)
C(14)	0.7262(4)	0.2647(8)	0.6625(3)	0.0198(9)
C(9)	0.1100(3)	0.1785(8)	0.6538(3)	0.0184(9)
C(12)	0.6354(3)	0.1531(7)	0.7609(3)	0.0121(8)
C(10)	0.1786(3)	0.0085(7)	0.6472(3)	0.0193(9)
C(17)	0.5708(3)	-0.0052(7)	0.6847(3)	0.0154(8)
C(13)	0.7118(3)	0.2881(8)	0.7486(3)	0.0159(8)
C(18)	0.8015(3)	0.0198(8)	1.0065(3)	0.0134(8)
N(1)	0.5148(2)	0.1409(6)	0.8411(2)	0.0106(6)
C(19)	0.8866(3)	-0.1274(8)	1.0183(3)	0.0193(9)
C(4)	0.6158(3)	-0.0879(8)	0.9855(3)	0.0151(9)
C(16)	0.5842(3)	-0.0342(8)	0.5984(3)	0.0183(9)
C(21)	1.0105(3)	0.1339(10)	1.1454(3)	0.0251(10)
C(20)	0.9904(4)	-0.0689(9)	1.0876(4)	0.0270(11)
C(8)	0.1458(3)	0.3932(8)	0.7044(3)	0.0189(9)

Table 3. Bond lengths [$\text{\AA}$] for **20**.

O(1)-C(1)	1.217(5)
Br(1)-C(15)	1.904(4)
Br(2)-C(9)	1.897(4)
O(3)-C(5)	1.215(5)
C(7)-C(6)	1.392(5)
C(7)-C(8)	1.400(6)
C(11)-C(10)	1.385(5)
C(11)-C(6)	1.393(6)
C(22)-C(23)	1.385(6)
C(22)-C(21)	1.387(7)

C(15)-C(14)	1.383(6)
C(15)-C(16)	1.392(6)
C(23)-C(18)	1.400(7)
C(5)-N(1)	1.405(5)
C(5)-C(6)	1.478(6)
O(2)-C(3)	1.415(5)
C(1)-N(1)	1.409(5)
C(1)-C(4)	1.498(5)
C(2)-N(1)	1.488(5)
C(2)-C(12)	1.508(5)
C(2)-C(3)	1.570(5)
C(3)-C(18)	1.516(5)
C(3)-C(4)	1.533(6)
C(14)-C(13)	1.389(6)
C(9)-C(8)	1.374(6)
C(9)-C(10)	1.381(6)
C(12)-C(13)	1.384(5)
C(12)-C(17)	1.393(5)
C(17)-C(16)	1.387(6)
C(18)-C(19)	1.389(6)
C(19)-C(20)	1.385(6)
C(21)-C(20)	1.364(7)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2$) for **20**.

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
O(1)	0.0147(15)	0.0153(15)	0.0183(16)	-0.0004(11)	0.0100(13)	0.0001(11)
Br(1)	0.0214(2)	0.0429(3)	0.0146(2)	-0.00442(17)	0.01108(17)	-0.00423(18)
Br(2)	0.01091(19)	0.0395(3)	0.0217(2)	0.0039(2)	0.00318(16)	-0.00249(19)
O(3)	0.0155(14)	0.0140(14)	0.0151(14)	0.0001(11)	0.0061(12)	-0.0013(11)
C(7)	0.017(2)	0.016(2)	0.011(2)	0.0000(15)	0.0043(17)	0.0029(16)
C(11)	0.0129(18)	0.016(2)	0.018(2)	-0.0011(16)	0.0051(16)	0.0023(16)
C(22)	0.019(2)	0.020(2)	0.016(2)	-0.0032(17)	0.0018(19)	-0.0097(18)
C(15)	0.0167(18)	0.025(2)	0.0105(18)	0.0027(17)	0.0074(15)	0.0023(18)
C(23)	0.017(2)	0.017(2)	0.014(2)	0.0009(17)	0.0042(17)	0.0019(17)
C(5)	0.012(2)	0.016(2)	0.009(2)	0.0006(14)	0.0044(16)	0.0016(15)
O(2)	0.0136(14)	0.0122(14)	0.0200(16)	-0.0024(11)	0.0058(13)	0.0004(11)
C(1)	0.016(2)	0.0107(19)	0.012(2)	-0.0031(14)	0.0083(16)	0.0007(15)
C(2)	0.0074(16)	0.0113(19)	0.016(2)	0.0011(15)	0.0048(15)	-0.0009(14)
C(6)	0.0109(19)	0.0138(19)	0.011(2)	0.0032(15)	0.0038(16)	0.0026(15)

C(3)	0.014(2)	0.0101(19)	0.012(2)	-0.0008(15)	0.0062(17)	0.0005(15)
C(14)	0.017(2)	0.027(2)	0.017(2)	0.0000(17)	0.0098(18)	-0.0037(18)
C(9)	0.0102(18)	0.028(2)	0.014(2)	0.0061(17)	0.0027(16)	-0.0030(16)
C(12)	0.0100(17)	0.0141(19)	0.0123(19)	0.0004(15)	0.0052(15)	0.0010(15)
C(10)	0.017(2)	0.015(2)	0.020(2)	0.0011(16)	0.0039(18)	-0.0008(16)
C(17)	0.016(2)	0.017(2)	0.014(2)	-0.0010(15)	0.0080(17)	-0.0043(15)
C(13)	0.0103(19)	0.022(2)	0.014(2)	-0.0026(16)	0.0047(17)	-0.0027(16)
C(18)	0.0113(19)	0.015(2)	0.0118(19)	0.0035(15)	0.0033(15)	-0.0003(15)
N(1)	0.0091(14)	0.0111(16)	0.0121(16)	-0.0001(13)	0.0053(12)	0.0009(13)
C(19)	0.017(2)	0.014(2)	0.024(2)	-0.0004(17)	0.0071(19)	0.0004(17)
C(4)	0.014(2)	0.016(2)	0.016(2)	0.0059(16)	0.0076(18)	0.0021(16)
C(16)	0.017(2)	0.023(2)	0.013(2)	-0.0045(16)	0.0055(17)	-0.0041(17)
C(21)	0.0120(19)	0.034(3)	0.021(2)	0.002(2)	-0.0002(17)	-0.006(2)
C(20)	0.010(2)	0.032(3)	0.034(3)	0.002(2)	0.006(2)	0.0044(19)
C(8)	0.013(2)	0.024(2)	0.019(2)	-0.0001(17)	0.0075(18)	0.0040(17)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2$) for **20**.

	x	y	z	U(eq)
H(7)	0.2812	0.5915	0.7796	0.019
H(11)	0.3352	-0.0613	0.6936	0.020
H(22)	0.9413	0.4263	1.1730	0.025
H(23)	0.7674	0.3297	1.0586	0.021
H(2)	0.6297	-0.3162	0.8529	0.024
H(2A)	0.657(4)	0.321(8)	0.892(3)	0.014
H(14)	0.7775	0.3563	0.6545	0.024
H(10)	0.1521	-0.1337	0.6111	0.023
H(17)	0.5179	-0.0927	0.6918	0.019
H(13)	0.7542	0.3961	0.7988	0.019
H(19)	0.8739	-0.2664	0.9794	0.023
H(4A)	0.6177	-0.2563	1.0041	0.018
H(4B)	0.6400	0.0099	1.0460	0.018
H(16)	0.5418	-0.1420	0.5481	0.022
H(21)	1.0803	0.1702	1.1925	0.030
H(20)	1.0468	-0.1687	1.0948	0.032
H(8)	0.0981	0.5029	0.7091	0.023

Table 6. Torsion angles ($^\circ$) for **20**.

C(6)-C(7)-C(8)	119.9(4)
C(10)-C(11)-C(6)	120.4(4)
C(23)-C(22)-C(21)	119.4(4)
C(14)-C(15)-C(16)	121.9(4)
C(14)-C(15)-Br(1)	120.8(3)

C(16)-C(15)-Br(1)	117.3(3)
C(22)-C(23)-C(18)	120.8(4)
O(3)-C(5)-N(1)	119.9(4)
O(3)-C(5)-C(6)	122.7(4)
N(1)-C(5)-C(6)	117.4(3)
O(1)-C(1)-N(1)	126.2(4)
O(1)-C(1)-C(4)	126.8(4)
N(1)-C(1)-C(4)	106.9(3)
N(1)-C(2)-C(12)	111.2(3)
N(1)-C(2)-C(3)	103.5(3)
C(12)-C(2)-C(3)	113.5(3)
C(7)-C(6)-C(11)	119.8(4)
C(7)-C(6)-C(5)	119.6(4)
C(11)-C(6)-C(5)	120.5(4)
O(2)-C(3)-C(18)	108.0(3)
O(2)-C(3)-C(4)	109.9(3)
C(18)-C(3)-C(4)	113.2(3)
O(2)-C(3)-C(2)	111.4(3)
C(18)-C(3)-C(2)	112.0(3)
C(4)-C(3)-C(2)	102.3(3)
C(15)-C(14)-C(13)	118.5(4)
C(8)-C(9)-C(10)	122.4(4)
C(8)-C(9)-Br(2)	119.3(3)
C(10)-C(9)-Br(2)	118.3(3)
C(13)-C(12)-C(17)	119.3(4)
C(13)-C(12)-C(2)	120.0(3)
C(17)-C(12)-C(2)	120.6(3)
C(9)-C(10)-C(11)	118.7(4)
C(16)-C(17)-C(12)	120.9(4)
C(12)-C(13)-C(14)	121.0(4)
C(19)-C(18)-C(23)	118.4(4)
C(19)-C(18)-C(3)	121.1(4)
C(23)-C(18)-C(3)	120.5(4)
C(5)-N(1)-C(1)	124.1(3)
C(5)-N(1)-C(2)	118.5(3)
C(1)-N(1)-C(2)	112.5(3)
C(20)-C(19)-C(18)	120.5(4)
C(1)-C(4)-C(3)	106.3(3)
C(17)-C(16)-C(15)	118.3(4)
C(20)-C(21)-C(22)	120.4(4)
C(21)-C(20)-C(19)	120.5(4)
C(9)-C(8)-C(7)	118.6(4)

Selected NMR Spectra

