A Transient N-O Linked Pauson-Khand Strategy for the Synthesis of the Deschloro Carbocyclic Core of the Palau'amines and Styloguanidines

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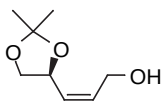
Supporting Information

Experimental procedures and characterization data for compounds **10**, **11**, **13-15**, and **17-22**

(10 pages)

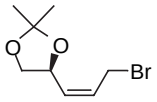
General experimental details: Solvents and reagents were used as received from the Aldrich Chemical Company, Inc., Fisher Scientific, Acros Organics, Mallinckrodt Baker, Inc., EM Science, Alfa Aesar, and Pharmco Products, Inc. The reactions were stirred magnetically and cooling was achieved using ice/brine, ice/water and dry ice/isopropanol baths. Organic phases were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate (Mallinckrodt Baker, Inc). Whatman filter paper and Celite® 545 were used for filtrations and evaporation of solvents was achieved on a Büchi rotary evaporator connected to a water aspirator for reduced pressure. TLC analysis was performed on Si250F glass coated plates with a 254 nm fluorescent indicator as supplied by J.T. Baker, Inc. Column chromatography was accomplished on 230-400 mesh, pH 6.5-7.0, 10% H_2O suspension, 60 Å silica gel from Silicycle, Inc. Optical rotations were determined with a Perkin Elmer Polarimeter 341. IR spectra were recorded on a MIDAC M1200 FTIR spectrometer. Proton (^1H) and carbon (^{13}C) NMR spectra were completed on QE plus 300-MHz and Bruker Avance 400- and 500-MHz spectrometers in $CDCl_3$ (Cambridge Isotope Labs, Inc.) using the residual solvent signal as the internal standard (δ 7.26). Mass Spectral analyses were performed by the Mass Spectrometry Service at the University of Illinois at Urbana-Champaign, School of Chemical Science.

(2*Z*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (10) 

1.0 M diisobutyl aluminum hydride in hexane (70.4 mL) was added dropwise over 20 minutes to a solution of **9** (6.58 g, 35.34 mmol) in dichloromethane (100.0 mL) at –78°C. The reaction was

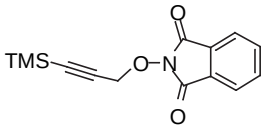
stirred for 4 hours, warming to room temperature before being cooled again to –78°C. To this a 1:1 triethylamine/water solution (45 mL) was added over 2 hours. The resulting white precipitate was filtered through Celite® 545 and thoroughly washed with dichloromethane. The filtrate was dried over sodium sulfate and evaporated *in vacuo* to yield a crude material that was purified by column chromatography on silica gel using hexanes/ethyl acetate (2:1) to furnish 5.08 g (91% yield) of the product **10** as a clear oil (R_f = 0.3 in 1:1 hexanes/ethyl acetate): IR (neat) 3403, 3023, 2987, 2937, 2874, 1456, 1381, 1373, 1247, 1216, 1157, 1058, 1031, 858 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.84 (m, 1H), 5.57 (m, 1H), 4.86 (m, 1H), 4.30 (m, 1H), 4.22 (m, 1H), 4.12 (dd, 1H, *J*=8.1, 6.1 Hz), 3.58 (t, 1H, *J*=7.9 Hz), 1.73 (bs, 1H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.3, 129.5, 109.5, 71.9, 69.6, 58.6, 26.8, 26.0. These data correspond to literature values.

(4*S*)-4-[(1*Z*)-3-bromoprop-1-enyl]-2,2-dimethyl-1,3-dioxolane (11)



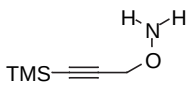
Carbon tetrabromide (1.96 g, 5.84 mmol) was added portionwise over 10 minutes to a solution of **10** (0.77 g, 4.87 mmol) and triphenylphosphine (1.55 g, 5.84 mmol) in dry acetonitrile (40.0 mL) at 0°C. This solution was stirred at 0°C for 5 minutes and then at room temperature for 30 minutes. The reaction mixture was then concentrated *in vacuo* and immediately purified by column chromatography using a hexanes/ethyl acetate gradient (loaded crude oil neat, 100:1 to 25:1) to furnish 1.05 g (97%) of the product **11** as a clear oil (R_f =0.65 in 2:1 hexanes/ethyl acetate): ^1H NMR ($CDCl_3$, 300 MHz) δ 5.81 (m, 1H), 5.49 (dd, 1H, *J*=10.7, 8.3 Hz), 4.79 (dd, 1H, *J*=14.4, 7.2 Hz), 4.05 (dd, 1H, *J*=8.2, 6.3 Hz), 3.97 (m, 1H), 3.87 (m, 1H), 3.47 (m, 1H), 1.32 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 132.2, 129.2, 109.6, 71.1, 69.0, 26.6, 25.9, 25.8. These data correspond to literature values.

2-{[3-(trimethylsilyl)prop-2-ynyl]oxy}-1*H*-isoindole-1,3(2*H*)-dione (13)



1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.92 mL, 6.13 mmol) was added dropwise to a yellow solution of 3-bromo-1-(trimethylsilyl)-1-propyne (0.87 mL, 6.13 mmol) and *N*-hydroxyphthalimide (1.00 g, 6.13 mmol) in dimethylformamide (30.0 mL) at room temperature. The resulting red solution was stirred for 20 minutes and then poured into 1N HCl (100 mL), stirred for several minutes and then filtered. The crude solid was purified by column chromatography on silica gel using diethyl ether as the eluent to give 1.68g (94%) of product **13** as a white solid: IR (neat) 2956, 2180, 1791, 1783, 1734, 1382, 1250, 976, 846, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (m, 2H), 7.78 (m, 2H), 4.87 (s, 2H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.3, 134.6, 128.8, 123.6, 97.5, 97.0, 65.7, -0.57. These data correspond to literature values.

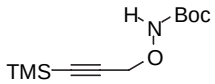
***O*-[3-(trimethylsilyl)prop-2-ynyl]hydroxylamine (14)**



Hydrazine (1.38 mL, 43.9 mmol) was added dropwise to a solution of **13** (10.0 g, 36.6 mmol) in anhydrous dichloromethane (200 mL) at room temperature and stirred for 12 hours. The reaction

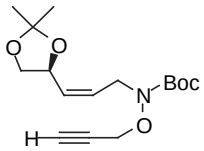
mixture was filtered to remove the white precipitate and the filtrate evaporated *in vacuo*. The crude mixture was purified by column chromatography on silica gel using hexanes/diethyl ether (1:1) as the eluent to give the product **14** 4.97 g (95%) as a clear oil (R_f = 0.6 in 1:1 hexanes/ethyl acetate): IR (neat) 3320, 3246, 3154, 2959, 2900, 2174, 1736, 1583. 1347, 1250, 1021, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.43 (s, 2H), 4.14 (s, 2H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 101.3, 91.2, 63.9, -0.24. These data correspond to literature values.

tert-butyl[3-(trimethylsilyl)prop-2-ynyl]oxycarbamate (15)

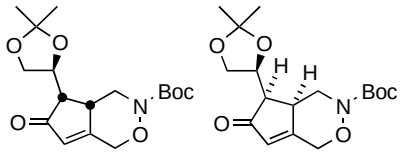


A solution of 1N sodium carbonate (Na_2CO_3 in 14.0 mL 1,4-dioxane) was added dropwise at room temperature to a solution of **14** (2.00 g, 14.0 mmol) and di-*t*-butyl dicarbonate (3.15 g, 14.4 mmol) in 1,4-dioxane (40.0 mL) and stirred for 12 hours. The reaction mixture was then concentrated *in vacuo*. After diluting with water, the mixture was adjusted to pH=4 by adding citric acid, extracted with dichloromethane (3x50 mL), dried with sodium sulfate and evaporated *in vacuo*. The crude cloudy oil was purified using column chromatography on silica gel with hexanes/ethyl acetate (7:1) as eluent to give 2.67 g (79%) of the product **15** as a clear oil (R_f = 0.5 in 7:1 hexane/ethyl acetate): IR (neat) 3284, 2977, 2967, 2181, 1733, 1724, 1368, 1251, 1168, 1108, 1034, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (s, 1H), 4.44 (s, 2H), 1.46 (s, 9H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 99.7, 92.8, 82.0, 64.5, 28.2, -0.24.; HRMS (FAB) *m/z* 244.1370 (MH^+, 244.1369 calcd for $C_{11}H_{22}NO_3Si$).

tert-butyl (2*Z*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl] prop-2-enyl (prop-2-ynyloxy) carbamate (17)



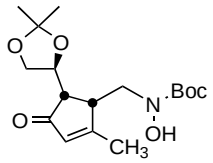
Sodium hydride (0.71 g, 17.75 mmol) was added at room temperature to a solution of **15** (2.86 g, 11.76 mmol), **11** (3.12 g, 14.11 mmol), and dimethylformamide (50.0 mL) and stirred for several minutes. The reaction mixture was heated to 50ºC for 12 hours, then cooled to room temperature. Water (30 mL) was added and the product was extracted with diethyl ether (4x50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. This crude reaction mixture (containing **16**) was dissolved in methanol (100.0 mL) and cooled to 0ºC. Anhydrous potassium carbonate (K_2CO_3, 1.95 g, 14.11 mmol) was added to the solution which was then allowed to warm to room temperature over 2 hours. After filtration through a silica plug and concentration, the crude material was purified by column chromatography on silica gel using a gradient of hexanes/ethyl acetate (5:1 to 2:1) to give 3.03 g (83%) of the product **17** as a clear oil: $[\alpha]^{20}_D$ –23.7 (*c* 0.02, $CHCl_3$); IR (neat) 3275, 3258, 2983, 2195, 1710, 1369, 1250, 1159, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.78 (m, 1H), 5.66 (dd, 1H, *J*=10.9, 8.4 Hz), 4.92 (dd, 1H, *J*=14.0, 7.8 Hz) 4.48 (m, 2H), 4.21 (d, 2H, *J*=7.9 Hz), 4.14 (dd, 1H, *J*=8.2, 6.2 Hz), 3.57 (t, 1H, *J*=8.0 Hz), 2.51 (t, 1H, *J*=2.4 Hz) 1.51 (s, 9H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 131.6, 127.2, 109.2, 82.0, 78.3, 75.4, 71.6, 69.3, 62.4, 47.6, 28.0, 26.6, 25.7; HRMS (FAB) *m/z* 312.1810 (MH^+, 312.1811 calcd for $C_{16}H_{26}NO_5$).



18a **18b**

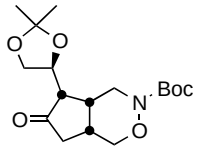
tert-butyl (4a*S*,5*S*)–5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-oxo-4,4a,5,6-tetrahydro cyclopenta[*d*][1,2]oxazine-3(1*H*)carboxylate (18a,b)

Dicobalt octacarbonyl ($Co_2(CO)_8$, 0.201 g, 0.558 mmol) was added at room temperature to a solution of **17** (0.167 g, 0.536 mmol) in anhydrous dichloromethane (50.0 mL) in a base-washed round bottom flask and stirred for 30 minutes until TLC showed complete formation of the red-brown alkyne-dicobalt intermediate. After bubbling N_2 through the brown reaction mixture for 30 minutes, the solution was cooled to 0°C and trimethylamine *N*-oxide (0.369 g, 4.72 mmol) was added. This reaction was allowed to warm to room temperature overnight during which time it turned intensely purple. Following dilution with ethyl acetate, the solution was filtered through a silica gel plug to remove the blue cobalt byproducts. After rinsing with ethyl acetate, it was concentrated *in vacuo*. The crude material was then purified by column chromatography on silica gel using a solvent gradient of hexanes/ethyl acetate (5:1 to 1:1) to give 0.126 g (69%) of a light yellow oil (**18a,b**, R_f = 0.4 in 1:1 hexanes/ethyl acetate) in a 4:1 diastereomeric ratio. **18a** (major): IR (neat) 2983, 2935, 1705, 1632, 1370, 1158, 1061 cm^{-1}; ^1H NMR (CDCl3, 400 MHz) δ 5.97 (s, 1H), 4.67 (s, 2H), 4.62 (q, 1H, J=6.2, 5.5, 4.8), 4.45 (dd, 1H, J=6.5), 3.95 (dd, 1H, J=7.0, 1.7), 3.49 (dd, 1H, J=6.1, 2.7), 3.12 (dd, 1H, J=10.9, 2.1), 2.96 (m, 1H), 2.56 (t, 1H, J=3.7), 1.45 (s, 9H), 1.42 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (CDCl3, 100 MHz) ppm 205.4, 172.3, 154.4, 128.7, 109.7, 82.9, 74. 4, 70.5, 65.8, 53.3, 52.5, 40.7, 28.7, 26.7, 24.7; HRMS (FAB) *m/z* 340.1760 (MH^+, 340.1760 calcd for $C_{17}H_{26}NO_6$). **18b** (minor): IR (neat) 2982, 2933, 2874, 1704, 1638, 1369, 1158, 1063 cm^{-1}; ^1H NMR (CDCl3, 400 MHz) δ 6.07 (s, 1H), 4.68 (s, 2H), 4.62 (q, 1H, J=6.2, 5.5, 4.8), 4.45 (dd, 1H, J=6.5), 3.95 (dd, 1H, J=7.0, 1.7), 3.49 (dd, 1H, J=6.1, 2.7), 3.12 (dd, 1H, J=10.9, 2.1), 2.96 (m, 1H), 2.57 (t, 1H, J=3.7), 1.45 (s, 9H), 1.42 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (CDCl3, 100 MHz) ppm 205.8, 173.3, 155.0, 128.6, 109.0, 82.8, 73.3, 70.5, 69.1, 51.8, 50.9, 41.8, 28.8, 27.3, 26.0; HRMS (FAB) *m/z* 340.1760 (MH^+, 340.1760 calcd for $C_{17}H_{26}NO_6$).



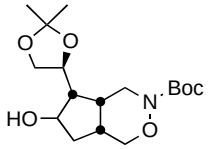
tert-butyl {(1*S*, 5*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-4-oxocyclo-pent-2-en-1-yl} methyl(hydroxy)carbamate (19)

To a stirred solution of cyclopentenone **18a,b** (0.04 g, 0.12 mmol) in dry THF (1.0 mL) under argon at room temperature was added 1 drop of EtOH. To this lightly yellow solution was added a 0.1 M solution of samarium diiodide (SmI_2) in THF (2.35 mL) during the addition of which the reaction turns a brighter yellow. After stirring for 30 minutes and TLC analysis, the reaction was quenched with a 10% aqueous sodium thiosulfate solution. Extraction with Et_2O (4x5mL), drying over $MgSO_4$, filtration and concentration *in vacuo* yields a crude material. After purification by column chromatography using a Hex/EtOAc gradient (3:1 to 1:2) the product **19** was obtained as a yellow oil (0.02 g, 49%, R_f = 0.4 in 1:2 Hex/EtOAc): IR (thin film) 3313 (br), 2981, 2934, 1733, 1698, 1618, 1393, 1369, 1250, 1216, 1160, 1113, 1058, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (bs, 1H), 5.94 (t, 1H, *J*=1.5 Hz), 4.69 (dt, 1H, *J*=7.1, 4.8 Hz), 4.07 (dd, 1H, *J*=21.2, 3.8 Hz), 3.89 (dd, 1H, *J*=8.5, 6.9 Hz), 3.37 (dd, 1H, *J*=8.5, 7.2 Hz), 3.32 (m, 1H), 3.02 (dd, 1H, *J*=4.8, 2.2 Hz), 2.94 (bd, 1H), 2.16 (s, 3H), 1.46 (s, 9H), 1.42 (s, 6H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.4, 179.3, 156.3, 132.1, 109.8, 82.1, 75.3, 65.3, 52.5, 52.1, 45.9, 28.7, 26.5, 24.7, 18.1; HRMS (FAB) *m/z* 342.1916 (MH^+, 342.1917 calcd for $C_{17}H_{28}NO_6$).



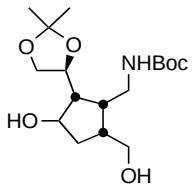
tert-butyl 5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]- 6-oxohexahydrocyclopenta [*d*][1,2]oxazine-3(1*H*)carboxylate (20)

Cyclopentenone **18** (0.052 g, 0.15 mmol) was dissolved in EtOH (5 mL). A catalytic amount of 10% palladium on carbon (Pd/C) was added and the reaction subjected to a 60 psi H_2 atmosphere in a Parr shaker for 10 hours. Filtration through Celite® 545 to remove the palladium and concentration *in vacuo* yielded crude product. Purification on silica gel using a Hex/EtOAc gradient (2:1 to 1:1) yields **20** as a clear oil (0.05 g, 95%, R_f = 0.4 in 1:2 Hex/EtOAc): IR (thin film) 2982, 2934, 2873, 1741, 1701, 1393, 1380, 1369, 1253, 1224, 1160, 1076, 1058, 918, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.33 (ddd, 1H, *J*=7.1, 7.1, 3.2 Hz), 3.90-4.04 (m, 3H), 3.75 (dd, 1H, *J*=13.9, 4.9 Hz), 3.65 (dd, 1H, *J*=13.9, 4.3 Hz), 3.61 (dd, 1H, *J*=12.2, 8.6 Hz), 2.67 (m, 1H), 2.51 (m, 1H), 2.33 (d, 1H, *J*=7.9 Hz), 2.30 (dd, 1H, *J*=18.7, 8.0 Hz), 2.11 (dd, 1H, *J*=18.2, 4.3 Hz) 1.44 (s, 9H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.5, 154.8, 109.1, 81.6, 75.1, 70.7, 65.8, 48.9, 46.2, 40.9, 36.2, 31.4, 28.1, 25.9, 25.2. HRMS (EI) *m/z* 241.1346 $(M(-Boc)^+$, 241.1314 calcd for $C_{12}H_{19}NO_4$).



tert-butyl (4a*R*,5*R*,7a*R*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]- 6-hydroxyhexahydrocyclopenta [*d*][1,2]oxazine-3(1*H*)carboxylate (21)

The saturated ketone **20** (0.31 g, 0.91 mmol) was dissolved in dry THF (4.0 mL) while under N_2. Prior to addition of $LiBH_4$ (0.07 g, 3.1 mmol) the solution was cooled to 0°C. After 1.5 hours, the reaction was warmed to room temperature and quenched with a pH 7 phosphate buffer, which causes the solution to bubble. After further dilution with H_2O, the reaction was extracted with Et_2O (4x3mL). The combined organic layers were washed with saturated sodium chloride solution before being concentrated to a crude oil. This material was dissolved in 4 mL of EtOH. 4 mL of 1N NaOH was added and the biphasic mixture refluxed for 20 minutes. After cooling, the mixture was quenched with 25mL 10% sodium bicarbonate solution. The reaction was extracted with Et_2O (5x3mL) and EtOAc (5x3mL) and the combined organic layers were dried over $MgSO_4$. Following filtration through Celite® 545, the solution was concentrated under reduced pressure to afford a cloudy oil. Column chromatography using a Hex/EtOAc gradient (loaded with CH_2Cl_2, 3:2 to 2:3) enabled isolation of the product alcohol **21** as a light yellow oil (mixture, 2:1 diastereomeric ratio, 0.250 g, 80%, R_f = 0.56 in EtOAc). The major diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.51 (dt, 1H, *J*=5.7, 2.5 Hz), 4.27 (m, 1H), 4.13 (dd, 1H, *J*=8.2, 6.0 Hz), 4.02 (dd, 1H, *J*=12.0, 5.4 Hz), 3.74 (app t, 1H, *J*=7.7 Hz), 3.70 (m, 1H), 3.68 (m, 1H), 3.45 (dd, 1H, *J*=14.0, 6.0 Hz), 2.70 (bs, 1H), 2.50 (dd, 1H, *J*=12.6, 7.0 Hz), 2.12 (m, 1H), 1.94 (dt, 1H, *J*=8.1, 5.8 Hz) 1.81 (m, 2H), 1.44 (s, 9H), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 109.2, 82.0, 76.3, 73.8, 72.2, 69.1, 48.9, 46.7, 37.2, 35.9, 35.4, 28.7, 27.2, 25.8.

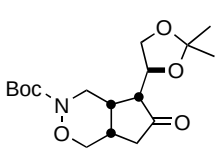


tert-butyl [(1*R*,2*R*,5*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]- 3-hydroxy-5-(hydroxymethyl)cyclopentyl] methylcarbamate (22)

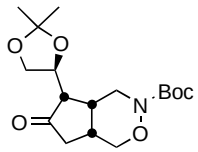
Method A: The saturated alcohol **21** (0.067 g, 0.195 mmol) was dissolved in dry THF (3.0 mL) under argon. HPLC grade H_2O (0.3 mL) was added to the solution prior to dropwise addition of a ~0.1 M solution of SmI_2 in THF. Slow addition of reagent was continued until the blue color failed to dissipate (approx. fifteen minutes). The reaction was allowed to stir at room temperature for 2 hours before being diluted with CH_2Cl_2 and quenched with a 10% sodium thiosulfate solution. Extraction with CH_2Cl_2 (4x3mL) was followed by washing the combined organic layers with saturated sodium chloride solution. After drying over Na_2SO_4, the solution was concentrated to a yellow oil. Purification by column chromatography using a Hex/EtOAc gradient (loaded with CH_2Cl_2, 10:1 to 100% EtOAc) provided the desired material **22** as a yellow oil (0.048 g, 71%).

Method B: The alcohol **21** (0.057 g, 0.166 mmol) was dissolved in dry EtOH (2.0 mL) under argon. Sodium hydrogen phosphate (0.111 g, 0.78 mmol) was added and the reaction cooled to 0°C. Excess sodium mercury amalgam (>0.85 g, >15% wt) was added and the reaction allowed to stir at 0°C for 8 hours. The reaction was diluted with THF, filtered through Celite® 545 and concentrated under reduced pressure. Purification on silica gel using a $CHCl_3$/MeOH gradient ($CHCl_3$ to 8:1 $CHCl_3$/MeOH) afforded product **22** as a yellow foam (0.044 g, 77%): IR (thin film) 3343 (br), 2977, 2926, 1688, 1529, 1367, 1270, 1251, 1169, 1046, 1017, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.40 (bs, 1H), 4.15 (m, 2H), 4.10 (dd, 1H, *J*=7.8, 6.4 Hz), 3.78 (m, 1H), 3.75 (m, 1H), 3.72 (m, 1H), 3.29 (dd, 1H, *J*=13.6, 8.2 Hz), 3.21 (dd, 1H, *J*=13.8, 5.9 Hz), 2.90 (bs, 1H), 2.60 (bs, 1H), 2.24 (m, 1H), 2.10 (dt, 1H, *J*=13.8, 7.0 Hz), 2.03 (dd, 1H, *J*=8.2, 5.7 Hz), 1.79 (dt, 1H, *J*=8.4, 5.8 Hz), 1.52 (dt, 1H, *J*=13.2, 5.9 Hz), 1.44 (s, 9H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.6, 109.1, 78.0, 75.0, 68.4, 63.5, 54.3, 43.0, 41.6, 38.2, 31.3, 30.1, 28.9, 26.9, 25.7. HRMS (FAB) *m/z* 346.2228 (MH^+, 346.2230 calcd for $C_{17}H_{32}NO_6$).

Absolute stereochemistry of the Pauson-Khand cyclization, based on the assignment of *tert*-butyl 5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]- 6-oxohexahydrocyclopenta [*d*][1,2]oxazine-3(1*H*)carboxylate (20).



20b



20a

In order to assign the stereochemistry of the major Pauson-Khand cyclization product **18**, and the hydrogenated cyclopentanone **20**, we performed an NOE analysis on ketone **20**. Since our mannitol starting material is enantiomerically pure and the relative stereochemistry of the cyclopentenone is set by the cis geometry of the olefin (in enyne **17**), only two potential diastereomers of **18** (**18a** or **18b**, shown in the main text), can be formed. An observed NOE between the bridgehead protons in ketone **20** confirmed the syn orientation of the ring substitution after hydrogenation (either **20a** or **20b**). Additionally, an observed NOE between the acetonide side-chain protons and several main chain protons in ketone **20** allowed us to confirm the stereochemistry of the Pauson-Khand cyclization with respect to the chirality of the mannitol-derived acetonide side-chain. The ^{1}H assignment for ketone **20** and the NOE analysis are shown below.

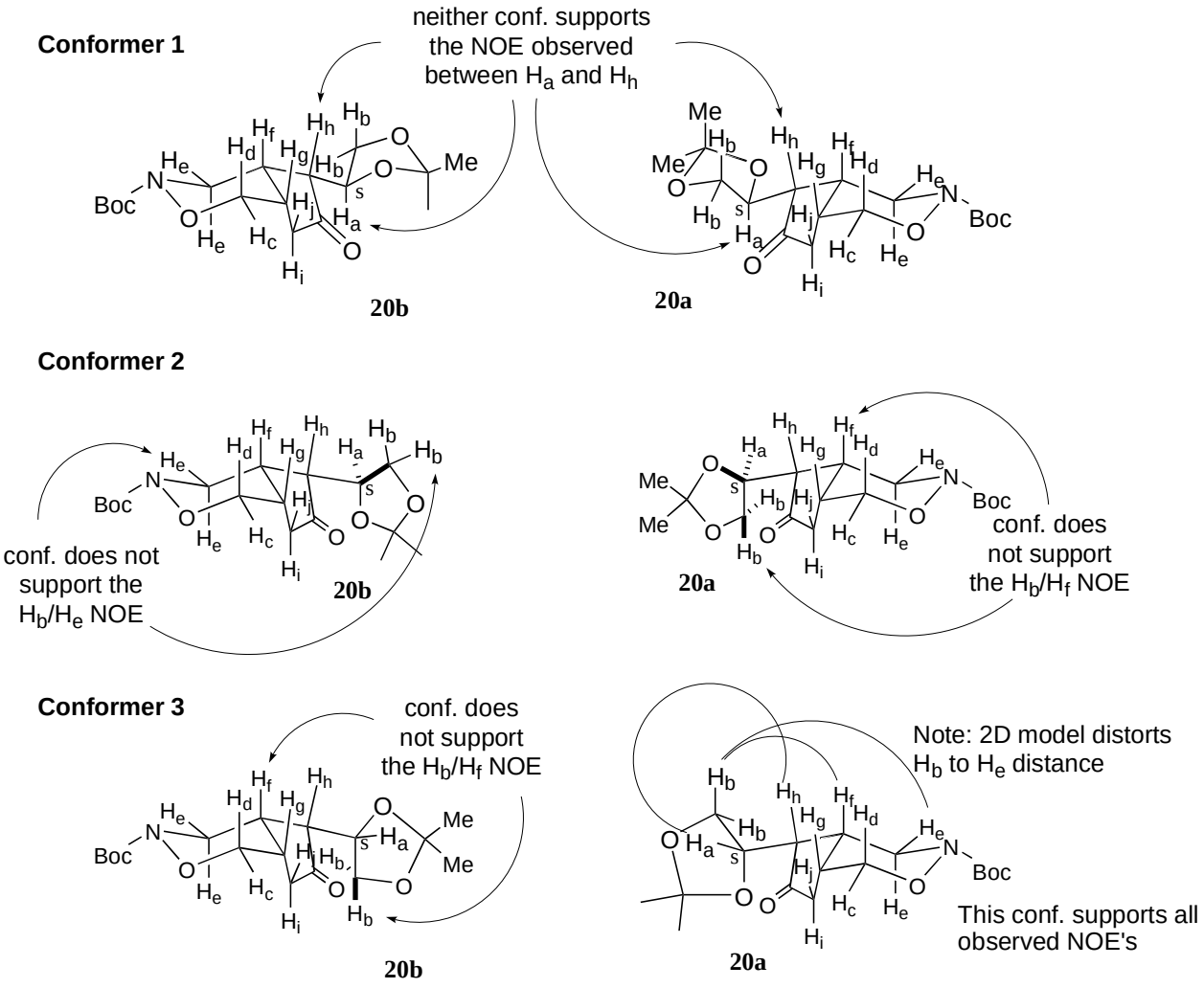
Proton assignments for cyclopentanone 20

Proton	**δ (ppm)**	**Peak**	**No. protons**	***J* (Hz)**	**NOE observed**
a	4.33	ddd	1 H	13.9 and 4.9	b, h
b_1,b_2	3.90 - 4.04	m	2 H	-	a, e, f
c	3.92 - 3.99 (est.)	m	1 H		
d	3.75	dd	1 H	13.9 and 4.9	
e_1	3.65	dd	1 H	13.9 and 4.3	b
e_2	3.61	dd	1 H	12.2 and 8.6	b
f	2.67	m	1 H	-	b, e, g, h
g	2.51	m	1 H	-	f
h	2.33	d	1 H	7.9	a, j, f
i	2.30	dd	1 H	18.7 and 8.0	
j	2.11	dd	1 H	18.2 and 4.3	h

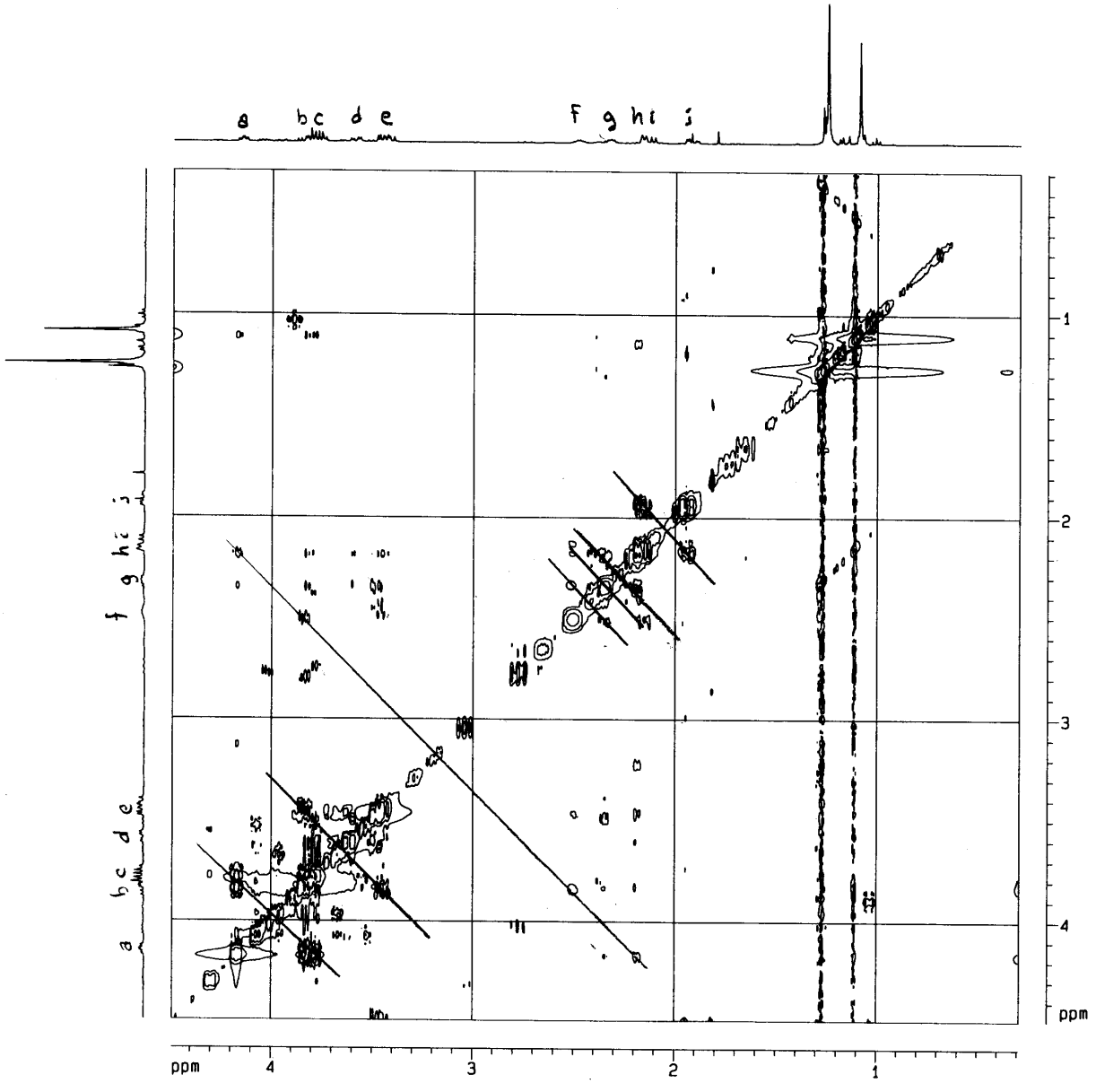
Assignment Note. Protons H_b and H_c are overlapped in the ^{1}H-NMR, with the resonance for proton c falling within the range of that for protons H_b. This and all other proton assignments were made with the aid of ^{1}H/^{1}H-COSY and ^{1}H/^{13}C-HETCOR spectra (not shown). The reported ^{1}H-NMR for compound **20** was obtained at 500 MHz. The NOESY data (shown below) were obtained at 400 MHz.

Ring geometry. The NOE's observed between H_f/H_g and H_f/H_h support an all-syn cyclopentanone ring orientation.

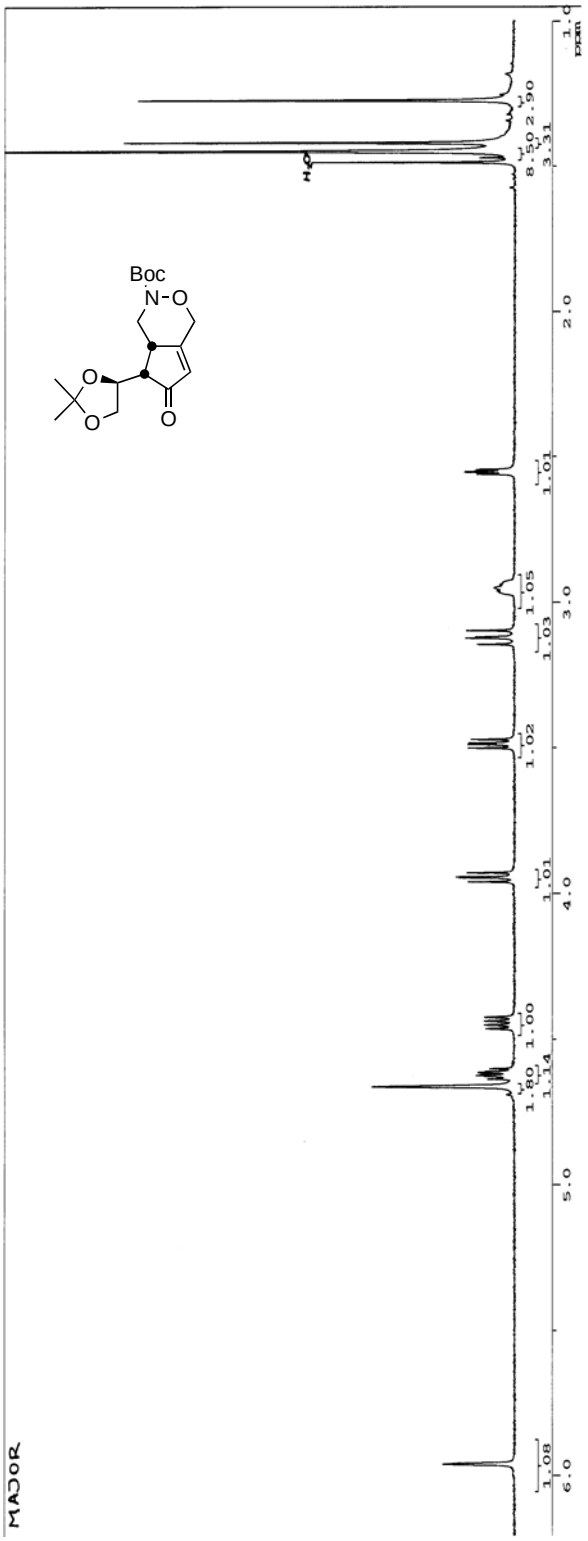
Absolute Stereochemistry. There are three possible conformations of the acetonide side chain relative to the main 5,6-ring system, each differing by a 120° rotation of the acetonide ring. Only conformer 3 of diastereomer **20a** supports all of the NOE's observed with respect to the acetonide side chain, particularly H_a/H_h, H_b/H_f and H_b/H_e (see structures and assignments below).



NOESY Spectra of *tert*-butyl 5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]- 6-oxohexahydrocyclopenta [*d*][1,2]oxazine-3(1*H*)carboxylate (20)



18a major diastereomer



18b minor diastereomer