Supporting Information

α,α -Disubstituted Boron Enolates in Asymmetric Synthesis of Quaternary Carbon Centers.

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Experimental Section

General Experimental. All reagents were commercial materials and were used without further purification with the following exceptions. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl, while toluene was distilled from calcium hydride. Alkylation and reductive enolization/trapping substrates were dried via azeotropic distillation of water using dry toluene. All aldehydes used were distilled neat and stored over 4 Å molecular sieves. All Schlenk flasks and lithium chloride were flamed-dried under vacuum. Alkyl halides were passed over basic alumina prior to addition. All dialkylboronhalides and triflates were distilled upon preparation. Chromatography was conducted using 230-400 mesh silica gel. NMR spectra were recorded at 300 or 400 MHz for ^1H and 75 or 100 MHz for ^{13}C . GC analyses were conducted on a CP Chirasil-dex column (25 m x 0.25 mm) using He (14 psi) as carrier gas. HPLC analyses were conducted on a Chiracel OD Column. High resolution mass spectrometry was performed by the Université de Sherbrooke, QC, Canada. The Université de Montréal, QC, CANADA, performed crystallographic analysis.

Preparation of Lithium di-tert-butylbiphenylide (LDBB).

Lithium (1.1 equiv.) was pressed into thin sheets, rinsed sequentially in hexanes, tetrahydrofuran, methanol and tetrahydrofuran and then added to a solution of di-tert-butyl biphenyl (1.0 eq) in tetrahydrofuran (50.0 mL) at 0 °C. The resulting solution was stirred for 5 hours before use. The reagent can be stored at 0 °C for 1 week. Stirring increases the lifetime of the reagent to 2 weeks at 0 °C.

Procedure for the synthesis of dicyclohexylboron bromide.

H. Brown, K. Ganesan, R. Dhar *J. Org. Chem.* **1993** 58 147-153

A 1.0 M solution of monobromoborane dimethyl sulfide complex (67.6 mL, 1.0 equiv.) in methylene chloride was added to a solution of cyclohexene (8.0 mL, 2.19 equiv.) in methylene chloride (5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 3 h. The reaction was then allowed to stand overnight at room temperature. The methylene chloride was then carefully removed using a vacuum pump. The remaining solid was recrystallized using dry hexanes and the material was allowed to stand overnight under argon. Excess hexanes was removed using a glass syringe. The remaining solid material was melted and then distilled under vacuum (bp = 108 °C at 1 mm Hg) to provide the desired product as a clear, colourless liquid, which was then stored under argon in the fridge.

Sample procedure for formation of dialkylated lactam starting material (3*S*, 7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (1a).

A 2.67M solution of n-butyllithium in hexanes (544 μL , 1.1 equiv.) was added to slurry of diisopropylamine (213 μL , 1.15 equiv.) and lithium chloride (279 mg, 5.0 equiv.) in THF at -78°C . After 30 minutes, a solution of (7S)-1-aza-4-thiabicyclo[5.3.0]-2-decanone (226 mg, 1.0 equiv.) in THF was added via cannula. The resulting mixture was stirred for 30 minutes, at which time ethyl iodide (116 μL , 1.05 equiv.) was added dropwise. The solution was warmed to -40°C and stirring was continued for 3 h, until TLC showed no reaction progress. Saturated aqueous ammonium chloride (5 mL) was added and the resulting mixture was warmed to 23°C and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 40 % ethyl acetate in hexanes to afford (3R, 7S)-1-aza-3-ethyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 80 % yield. The second alkylation was performed as follows – a solution of 2.67 M n-butyllithium in hexanes (441 μL , 1.1 equiv.) was added to slurry of diisopropylamine (172 μL , 1.15 equiv.) and lithium chloride (227 mg, 5.0 equiv.) in THF at -78°C . After 30 minutes, a solution of (3R, 7S)-1-aza-3-ethyl-4-thiabicyclo[5.3.0]-2-decanone (214 mg, 1.0 equiv.) in THF was added via cannula. The resulting mixture was stirred for 30 minutes, at which time methyl iodide (133 μL , 2.0 equiv.) was added dropwise. Stirring was continued for 3 h, until TLC showed no reaction progress. Saturated aqueous ammonium chloride (5 mL) was added and the resulting mixture was warmed to 23°C and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford (3S, 7S)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 89 % yield. ^1H NMR (CDCl_3) δ 4.52 (m, 1H), 3.44-3.59 (m, 2H), 2.84 (m, 1H), 2.63 (m, 1H), 2.08-2.17 (m, 2H), 1.73-

1.83 (m, 4H), 1.58-1.71 (m, 2H), 1.48 (s, 3H), 1.02 (t, 3H); ^{13}C NMR (CDCl_3) δ 171.7, 55.7, 53.2, 48.4, 35.8, 33.9, 32.6, 28.3, 25.8, 21.5, 9.5. The product was determined to have > 99 % de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 $^\circ\text{C}$, R_t = 15.7 minutes (minor diastereomer), 16.3 minutes (major diastereomer)).

Synthesis of (3*S*, 7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone.

The alkylation was carried out at $-78\text{ }^\circ\text{C}$ over 3 h using benzyl bromide (156 μL , 1.1 equiv.). The reaction was purified by chromatography on silica gel eluting with 40 % ethyl acetate in hexanes to afford (3*R*, 7*S*)-1-aza-3-benzyl-4-thiabicyclo[5.3.0]-2-decanone as a white solid in 90 % yield. The second alkylation was also carried out at $-78\text{ }^\circ\text{C}$ over 3 h using methyl iodide (73 μL , 1.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford (3*S*, 7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil. ^1H NMR (CDCl_3) δ 7.35-7.38 (m, 2H), 7.10-7.21 (m, 3H), 4.53 (m, 1H), 3.57 (d, 1H, J = 13.2 Hz), 3.40-3.53 (m, 2H), 2.82 (d, 1H, J = 13.2 Hz), 2.45 (m, 1H), 1.93-2.05 (m, 2H), 1.38-1.77 (m, 8H); ^{13}C NMR (CDCl_3) δ 171.7, 138.1, 132.0, 127.6, 126.5, 55.8, 54.2, 49.1, 48.0, 33.8, 32.8, 28.0, 26.7, 21.7. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NOS}$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.68; H, 7.64; N, 5.06. The product was determined to have >99 % de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 $^\circ\text{C}$, R_t = 18.9 minutes (minor diastereomer), 19.7 minutes (major diastereomer)).

Synthesis of (3*S*, 7*S*)-1-aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone.

The alkylation was carried out at -78°C over 3 h using allyl bromide (121 μL , 1.1 equiv.). The reaction was purified by chromatography on silica gel eluting with 40 % ethyl acetate in hexanes to afford (3R, 7S)-1-aza-3-allyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 86 % yield. The second alkylation was also carried out at -78°C over 3 h using methyl iodide (90 μL , 1.5 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford (3S, 7S)-1-aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 85 % yield. ^1H NMR (CDCl_3) δ 5.95 (m, 1H), 5.04-5.13 (m, 2H), 4.43 (m, 1H), 3.48-3.54 (m, 2H), 2.78-2.87 (m, 2H), 2.63 (m, 1H), 2.42 (dd, 1H, $J = 7.8, 13.1$ Hz), 2.12 (m, 1H), 1.61-1.86 (m, 5H), 1.49 (s, 3H); ^{13}C NMR (CDCl_3) δ 172.1, 135.2, 118.4, 56.2, 51.8, 49.0, 47.0, 34.7, 33.5, 28.4, 25.1, 21.8. Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NOS}$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.68; H, 7.64; N, 5.06. The product was determined to have >95 % de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170°C , $R_t = 14.7$ minutes (minor diastereomer), 15.5 minutes (major diastereomer)).

Formation of (2S)-N-((2R, 3S)-2-ethyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine from (3S, 7S)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (5a).

A solution of LDBB in THF was added dropwise via gas syringe to a solution of lactam (99.3 mg, 1.0 equiv.) in THF in a Schlenk flask at -78°C until the green colour of LDBB persisted. Dicyclohexylboron bromide (203 μL , 2.0 equiv.) was then immediately added dropwise via syringe. The solution colour changed from green to red and this solution was stirred for 30 min at -78°C . Benzaldehyde (95 μL , 2.0 equiv.) was then added dropwise and the resulting mixture was stirred for 2 h at -78°C , at which point a saturated solution of ammonium chloride was added to quench the reaction. The product was extracted using ethyl acetate (3 x 20 mL) and the organic layer was dried with anhydrous sodium sulfate. Boron decomplexation was accomplished by stirring the crude product with diethanolamine (196 μL , 4.4 equiv.) in diethyl ether (10 mL) for 2 h at room temperature. The organic layer was then extracted from the solid material using a pipette and the ether was removed using the rotary evaporator. The solid crude material was suspended in reagent grade methanol (15 mL). Benzyl bromide (68 μL , 1.2 equiv.) and 2 M NaOH (349 μL , 1.5 equiv.) were added and the reaction was stirred for 45 min at room temperature. The reaction was quenched with saturated ammonium chloride solution and the material extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with distilled water (1 x 30 mL) and dried over anhydrous sodium sulfate. The material was purified by column chromatography by elution with 10-20 % ethyl acetate/hexanes to afford 154 mg of product (81 % yield). ^1H NMR (CDCl_3 , 23°C) δ 7.22-7.37 (m, 10 H), 4.96 (m, 1H), 4.27 (m, 1H), 3.94 (m, 1H), 3.74 (m, 2H), 3.28 (m, 2H), 2.38-2.42 (t_{obs} , 2H, $J_{\text{obs}} = 7.7$ Hz), 2.19 (m, 1H), 1.88-2.07 (m, 1H, $J = 7.2$ Hz), 1.4 –1.84 (m, 6H), 1.13 (s, 3H), 0.89-0.93 (t_{obs} , 3H, $J_{\text{obs}} = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 23°C) δ 174.8, 140.4, 138.2, 128.7, 128.4, 128.0, 127.5, 127.4, 126.8, 79.9, 59.1, 52.3, 47.4, 47.2, 36.2, 29.8, 28.3, 28.2, 25.2, 21.2, 19.5, 10.1; HRCIMS m/z ($\text{M}+\text{H}$), 411.2232 $\text{C}_{25}\text{H}_{33}\text{NO}_2\text{S}^+$ requires 411.2224. The product was determined to have >94 % de (*syn*

isomer) and *syn:anti* isomer as determined by HPLC by elution with 4 % iPrOH/hexanes. Retention times were ratio 19.2 min, 21.6 min, 26.9 min, 48.7 min.

(2R, 3S)-2-ethyl-2-methyl-1,3-hydrocinnamyl alcohol via reduction of (2S)-N-((2R, 3S)-2-ethyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiaprolyl)-pyrrolidine

A solution of LDBB in THF was added dropwise via gas syringe to a solution of lactam (176.0 mg, 1.0 equiv.) in THF at -78 °C until the green colour of LDBB persisted. The aldol reaction was conducted as per usual using dicyclohexylboron bromide (359 µL, 2.0 equiv.) and benzaldehyde (168 µL, 2.0 equiv.). Boron decomplexation was accomplished by stirring the crude product with diethanolamine (316 µL, 4.4 equiv.) in diethyl ether (10 mL) for 2 h at room temperature. The material was purified by column chromatography by elution with 10-20 % ethyl acetate/hexanes to afford 207 mg of product (78 % yield). ¹H NMR (CDCl₃, 23 °C) δ 7.23-7.37 (m, 5H), 4.31 (bs, 1H), 3.79 (bs, 1H), 3.23-3.49 (m, 2H), 2.49-2.56 (q_{obs}, 2H, J_{obs} = 7.8), 1.45-2.16 (m, 8H), 1.15 (s, 3H), 0.90-0.95 (t_{obs}, 3H, J_{obs} = 7.5); ¹³C NMR (CDCl₃, 23 °C) δ 174.4, 140.7, 127.5, 127.2, 127.0, 79.1, 58.4, 52.8, 46.9, 37.9, 29.5, 28.2, 24.9, 21.5, 18.2, 9.6; HRCIMS *m/z* (M+H, 322.1841 C₂₅H₃₃NO₂S⁺ requires 322.18344. This material was then used for the borane-ammonia reduction. 2.57 M solution of n-butyllithium in hexanes (544 µL, 5.8 equiv.) was slowly added to a stirred solution of diisopropylamine (210 µL, 6.2 equiv.) in 1.0 mL tetrahydrofuran at 0 °C. After stirring for 10 minutes, borane-ammonia complex (45 mg, 6.0 equiv., 90 % tech. grade) was added in one portion. After stirring for 15 minutes at 0 °C, the

mixture was warmed to 23 °C and a solution of (2*S*)-*N*-(2*R*, 3*S*)-2-ethyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiopropyl)-pyrrolidine (78 mg, 1.0 equiv.) in 2.0 mL tetrahydrofuran was added via cannula. The mixture was heated to reflux for 24 hours, then cooled to 0 °C and quenched with aqueous hydrochloric acid (3 M, 3 mL). The resulting mixture was warmed to 23 °C and stirred for 30 minutes, at which point aqueous sodium hydroxide (3M, 6 mL) was added. The mixture was stirred at 23 °C for 30 minutes and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography using 10-20 % ethyl acetate/hexanes afforded 20 mg of diol (42 % yield). This material was then converted to the acetonide by stirring in 2,2-dimethoxypropane/DMF (3:2, 3 mL) with a catalytic amount of pyridium *p*-toluenesulfonate at room temperature for 12 h. The mixture was quenched by addition of saturated aqueous sodium bicarbonate and the product was extracted with 2:1 hexanes/ether. The combined organic layers were washed with water (2 x 10 mL), dried over sodium sulfate and concentrated in vacuo. Column chromatography on silica gel eluting 5 % ethyl acetate/hexanes afforded 22 mg of the desired acetonide (90 % yield). Isomer mixture: ¹H NMR (C₆D₆) δ (*syn* isomer) 7.293-7.297 (d, 2H, *J* = 1.6 Hz), 7.05-7.15 (m, 3H), 4.57 (s, 1H), 3.56-3.59 (d, 1H, *J* = 11.6 Hz), 3.35-3.59 (dd, 1H, *J* = 11.6 Hz, *J* = 1.2 Hz), 2.13-2.22 (dq, 1H, *J* = 7.2 Hz), 1.57 (s, 3H), 1.31 (s, 3H), 0.76-0.85 (ddq, 1H, *J* = 1.2 Hz, *J* = 7.2 Hz), 0.63- 0.66 (*t*_{obs}, 3H, *J*_{obs} = 7.2 Hz), 0.41 (s, 3H); ¹³C NMR (C₆D₆) δ 138.8, 128.3, 127.6, 127.4, 98.9, 81.0, 67.0, 36.7, 30.3, 22.0, 19.1, 18.7, 7.9; (*anti* Isomer) 7.295-7.298 (d, 2H, *J* = 1.53 Hz), 7.04- 7.15 (m, 3H), 4.55 (s, 1H), 3.56-3.59 (d, 1H, *J* = 11.5 Hz), 3.44-3.47 (d, 1H, *J* = 11.5 Hz), 1.58 (s, 3H), 1.31 (s, 3H), 0.92- 0.98 (m, 5H), 0.45-0.51 (*t*_{obs}, 3H, *J*_{obs} = 7.3 Hz); ¹³C NMR (C₆D₆) δ 139.1, 128.4, 127.6, 127.5, 98.9, 79.7, 69.9, 36.8, 30.2, 28.8, 19.2, 15.9, 7.1; HRCIMS *m/z* (M+H, 235.1698 C₁₅H₂₃O₂⁺ requires 235.1702.

Formation of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-3-(4-methoxyphenyl)propanoyl)-2-(4-phenyl-3-thiapropyl)pyrrolidine from (3*S*, 7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (5b).

The aldol reaction was carried out at -78 °C over 2 h using Cy2BBr (198 µL, 2.0 equiv.) and 4-methoxybenzaldehyde (110 µL, 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 164 mg of product (83 % yield). The product was determined to have a 91:9 *syn/anti* ratio with 98 % de (*syn* isomer) by HPLC analysis by eluting with 4 % ipropanol/hexanes. The retention times were: 30.9 min, 38.7 min, 40.1 min, 54.1 min. ¹H NMR (CDCl₃, 23 °C) δ 7.22-7.31 (m, 7H), 6.82-6.84 (d, 2H, J = 8.4 Hz), 4.91 (s, 1H), 4.17-4.26 (m, 1H), 3.94 (m, 1H), 3.61- 3.79 (m, 5H), 3.32-3.48 (m, 2H), 2.38-2.42 (t_{obs}, 2H, J_{obs} = 7.3 Hz), 2.13- 2.27 (m, 1H), 1.96-2.04 (m, 1H, J_{obs} = 6.9 Hz), 1.68-1.86 (m, 3H), 1.11 (s, 3H), 0.88-0.92 (t_{obs}, 3H, J_{obs} = 7.3 Hz); ¹³C NMR (CDCl₃, 23 °C) δ 175.0, 158.7, 138.2, 132.6, 129.0, 128.7, 128.3, 126.8, 112.9, 79.4, 59.0, 55.2, 52.3, 47.2, 36.1, 32.7, 28.3, 28.1, 25.2, 19.5, 10.1; HRCIMS *m/z* (M+H, 441.2337 C₂₆H₃₅NO₃S⁺ requires 441.2348.

Formation of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-3-(4-bromophenyl)-propanoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine from (3*S*, 7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (5c).

The aldol reaction was carried out at -78°C over 2 h using Cy₂BBr (201 μL , 2.0 equiv.) and 4-bromobenzaldehyde (171 mg, 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 184 mg of product (81 % yield). The product was determined to have a 93:7 *syn/anti* ratio with 99 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 21.1 min, 23.1 min, 27.3 min, 31.9 min. ¹H NMR (CDCl₃, 23 °C) δ 7.42-7.44 (d_{obs}, 2 H, $J_{\text{obs}} = 8.6$ Hz), 7.30-7.31 (m, 3 H), 7.23-7.25 (m, 4H), 4.93 (s, 1H), 4.09- 4.29 (m, 2 H), 3.75 (s, 2H), 3.34-3.37 (t_{obs}, 2H, $J_{\text{obs}} = 5.8$ Hz), 2.39-2.43 (t_{obs}, 2H, $J_{\text{obs}} = 7.4$ Hz), 2.18-2.21 (m, 1H), 1.72-1.97 (m, 4H), 1.40-1.53 (m, 3H), 1.10 (s, 3H), 0.89-0.92 (t_{obs}, 3H, $J_{\text{obs}} = 7.4$ Hz); ¹³C NMR (CDCl₃, 23 °C) δ 174.7, 139.6, 138.3, 130.6, 130.4, 129.8, 128.8, 128.4, 128.1, 126.8, 121.3, 79.4, 59.1, 52.0, 47.3, 36.3, 32.8, 28.3, 28.2, 28.0, 25.2, 19.7, 14.3, 10.1; HRCIMS m/z (M+H, 489.1337 C₂₅H₃₂BrNO₂S⁺ requires 489.1346.

Formation of (2*S*)-*N*-(*trans*-(2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-5-phenyl-pent-4-enoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine from (3*S*, 7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (5d).

The aldol reaction was carried out at -78°C over 2 h using Cy₂BBR (198 μL , 2.0 equiv.) and *trans*-cinnamaldehyde (115 μL , 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 126 mg of product (63 % yield). The product was determined to have a 91:9 *syn/anti* ratio with 99 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 39.6 min., 59.0 min., 60.0 min., 65.0 min. ¹H NMR (CDCl₃, 60 $^{\circ}\text{C}$) δ 7.19-8.30 (m, 10 H), 6.63-6.67 (m, 1H, $J = 15.9$ Hz), 6.33-6.39 (dd, 1H, $J_{\text{trans}} = 15.9$ Hz, $J = 6.7$ Hz), 4.41-4.42 (d, 1H, $J = 5.9$ Hz), 4.27-4.34 (m, 1H), 3.64-3.76 (m, 3 H), 3.43-3.55 (m, 1H), 2.42-2.46 (t_{obs} , 2H, $J_{\text{obs}} = 7.54$ Hz), 2.12-2.20 (m, 1H), 1.25–1.99 (m, 8H), 0.93-0.97 (t_{obs} , 3H, $J_{\text{obs}} = 7.54$ Hz); ¹³C NMR (CDCl₃, 23 $^{\circ}\text{C}$) δ 175.0, 138.2, 136.9, 132.0, 128.8, 128.6, 128.4, 128.35, 127.4, 126.8, 126.4, 79.0, 58.7, 50.9, 47.2, 36.1, 32.8, 28.3, 28.1, 27.6, 25.4, 9.9; HRCIMS m/z ($M+H$), 437.2388 C₂₇H₃₅NO₂S⁺ requires 437.2397.

Formation of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-4-methyl-pent-4-enoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine from (3*S*, 7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (5e).

The aldol reaction was carried out at -78°C over 2 h using Cy₂BBr (208 μL , 2.0 equiv.) and methacrolein (120 μL , 3.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 89 mg of product (49 % yield). The product was determined to have a 98:2 *syn/anti* ratio with 95 % de (*syn* isomer) by HPLC analysis by eluting with 2 % 2-propanol/hexanes. The retention times were: 17.0 min., 21.4 min., 22.7 min., 23.8 min. ¹H NMR (CDCl₃, 23 $^{\circ}\text{C}$) δ 7.20-7.35 (m, 5H), 4.98 (s, 2H), 4.22-4.27 (m, 2H), 3.62-3.77 (m, 2H), 3.45-3.51 (m, 1H), 2.38-2.42 (t_{obs}, 2H, J_{obs} = 7.3 Hz), 1.71-2.18 (m, 8H), 1.42-1.59 (m, 3H), 1.19-1.39 (m, 4H), 0.88-0.91 (t_{obs}, 3H, J_{obs} = 7.23 Hz); ¹³C NMR (CDCl₃, 23 $^{\circ}\text{C}$) δ 175.0, 145.1, 138.3, 128.8, 128.3, 126.8, 114.5, 80.9, 58.9, 51.0, 47.4, 36.1, 32.7, 28.6, 28.4, 28.1, 25.4, 20.8, 20.1, 9.8; HRCIMS *m/z* (M+H, 375.2232 C₂₂H₃₃NO₂S⁺ requires 375.2239.

Formation of (2*S*)-*N*-(*trans*-(2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-4-methyl-hex-4-enoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine from (3*S*, 7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (5f).

The aldol reaction was carried out at -78°C over 2 h using Cy₂BBr (350 μL , 2.0 equiv.) and 2.0 equiv. of tiglic aldehyde (233 μL , 3.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford the product in 95 % yield. The product was determined to have a 91:9 *syn/anti* ratio with 91 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 11.2 min., 12.8 min., 14.4 min., 15.7 min.. ¹H NMR (CDCl₃, 23 °C) δ 7.18- 7.51 (m, 5H), 5.46-5.51 (q_{obs}, 1H, J_{obs} = 6.4 Hz), 4.18-4.34 ((m, 2H), 6.65-3.79 (m, 3H), 3.43-3.59 (m, 1H), 2.40-2.44 (t_{obs}, 2H, J_{obs} = 7.73 Hz), 2.09-2.17 (m, 1H), 1.98-2.07 (m, 1H, J=7.3 Hz), 1.77-1.93 (m, 3H), 1.61-1.67 (m, 6H), 1.43-1.59 (m, 3H), 1.18 (s, 3H), 0.85-0.88 (t_{obs}, 3H, J_{obs} = 7.23 Hz); ¹³C NMR (CDCl₃, 23 °C) δ 175.1, 138.2, 135.3, 128.7, 128.3, 126.5, 123.6, 82.7, 58.9, 51.6, 47.4, 36.1, 32.7, 28.7, 28.4, 28.1, 25.4, 20.3, 14.1, 13.3, 9.8; HRCIMS *m/z* (M+H, 390.2467 C₂₃H₃₆NO₂S⁺ requires 390.2471.

Formation of (2*S*)-*N*-((2*R*, 3*S*)-2-benzyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine from (3*S*, 7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (5h).

The aldol reaction was carried out at -78 °C over 2 h using Cy₂BBR (159 µL, 2.0 equiv.) and benzaldehyde (74 µL, 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 158 mg of product (91 % yield). The product was determined to have a 91:9 *syn/anti* ratio with 99 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 24.2 min., 28.2 min., 31.5 min., 38.2 min. ¹H NMR (CDCl₃, 23 °C) δ 7.12-7.51 (m, 15H), 5.07 (s, 1H), 4.11-4.30 (m, 2H), 3.62-3.84 (m, 3H), 2.58-2.81 (m, 3H), 2.13-2.38 (m, 3H), 1.02-1.76 (m, 9H); ¹³C NMR (CDCl₃, 23 °C) δ 174.2, 140.6, 138.3, 138.1, 130.7, 128.8, 128.3, 127.9, 127.7, 127.6, 127.5, 126.8, 126.1, 79.2, 59.5, 53.7, 47.3, 42.5, 36.0, 31.9, 28.0, 27.7, 24.8, 18.2; HRCIMS *m/z* (M+H, 474.2467 C₃₀H₃₆NO₂S⁺ requires 474.2460.

Formation of (2*S*)-*N*-((2*R*, 3*S*)-2-allyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine from (3*S*, 7*S*)-1-aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (7g).

The aldol reaction was carried out at -78°C over 2 h using Cy₂BBR (196 μL , 2.0 equiv.) and benzaldehyde (137 μL , 3.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 136 mg of product (71 % yield). The product was determined to have a 92:8 *syn/anti* ratio with 91 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 18.5 min., 21.0 min., 24.5 min., 40.9 min. ¹H NMR (CDCl₃, 23 $^{\circ}\text{C}$) 7.10-7.37 (m, 10H), 5.75-5.85 (m, 1H), 4.98-5.05 (m, 3H), 4.25 (*s*_{obs}, 1H), 3.98 (*s*_{obs}, 1H), 3.75 (*s*_{obs}, 2H), δ 3.28-3.34 (m, 1H), 3.05-3.14 (m, 1H), 2.84-2.89 (dd, 1H, *J* = 4.32 Hz, 5.97 Hz) 2.37-2.2.41 (*t*_{obs}, 2H, *J*_{obs} = 7.5 Hz), 2.05-2.22 (m, 2H), 1.18-1.15 (m, 7H), ¹³C NMR (CDCl₃, 23 $^{\circ}\text{C}$) δ 174.4, 140.3, 138.3, 135.2, 128.7, 128.3, 128.0, 127.6, 127.4, 126.8, 117.0, 79.3, 59.0, 51.9, 47.3, 40.6, 36.2, 32.7, 28.3, 28.1, 25.1, 19.2; HRCIMS *m/z* (*M*+H, 424.2310 C₂₆H₃₄NO₂S⁺ requires 424.2314.

X-ray Crystal Structure and Data for:

Crystal Data

C₁₈H₂₇NO₂S

$M_r = 321.47$

Orthorhombic

$P2_{12121}$

$a = 10.6580(5) \text{ \AA}$

$b = 11.8382(6) \text{ \AA}$

$c = 13.8053(7) \text{ \AA}$

$V = 1741.84(15) \text{ \AA}^3$

$Z = 4$

$D_x = 1.226 \text{ Mg m}^{-3}$

D_m not measured

Cu $K\alpha$ radiation

$\lambda = 1.54178 \text{ \AA}$

Cell parameters

$\theta = 3.20\text{-}72.64^\circ$

$\mu = 1.696 \text{ mm}^{-1}$

$T = 220(2) \text{ K}$

Platelet

Colourless

0.60 x 0.14 x 0.06 mm

Table 1: Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

$$U_{eq} = (1/3) \sum_i \sum_j U^{ij} a^i a^j \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	U_{eq}
S1	0.91379(7)	-0.02434(6)	0.95922(6)	0.0619(2)
H1	0.888(3)	0.059(3)	1.006(2)	0.094(11)
C1	0.9049(2)	0.0473(2)	0.84323(18)	0.0505(6)
H1A	0.9799	0.0942	0.8348	0.061
H1B	0.9043	-0.0092	0.7913	0.061
C2	0.7891(2)	0.12100(17)	0.83425(17)	0.0408(5)
H2A	0.7905	0.1783	0.8855	0.049
H2B	0.7142	0.0743	0.8438	0.049
C3	0.7804(2)	0.17956(17)	0.73636(17)	0.0396(5)
H3	0.7856	0.1228	0.6838	0.048
C4	0.8826(2)	0.26991(19)	0.7221(2)	0.0508(6)
H4A	0.9245	0.2868	0.7836	0.061
H4B	0.9456	0.2441	0.6754	0.061

C5	0.8142(2)	0.3734(2)	0.6841(2)	0.0585(7)
H5A	0.8577	0.4429	0.7032	0.070
H5B	0.8072	0.3712	0.6134	0.070
C6	0.6872(2)	0.36600(17)	0.73105(19)	0.0458(6)
H6A	0.6895	0.3941	0.7978	0.055
H6B	0.6244	0.4086	0.6944	0.055
N1	0.66119(16)	0.24371(13)	0.72815(13)	0.0361(4)
C7	0.55258(19)	0.18827(15)	0.71348(14)	0.0336(4)
O7	0.55311(14)	0.08422(10)	0.70525(11)	0.0413(4)
C8	0.42658(19)	0.25360(15)	0.71139(15)	0.0364(5)
C9	0.40574(19)	0.31279(15)	0.81189(16)	0.0365(4)
H9	0.4798	0.3607	0.8253	0.044
O9	0.29829(14)	0.38409(11)	0.80803(14)	0.0501(4)
H9A	0.3208	0.4504	0.7991	0.075
C10	0.3925(2)	0.22921(16)	0.89411(16)	0.0387(5)
C11	0.2771(2)	0.18188(19)	0.9187(2)	0.0486(6)
H11	0.2040	0.2051	0.8863	0.058
C12	0.2698(3)	0.1004(2)	0.9912(2)	0.0582(7)
H12	0.1918	0.0679	1.0064	0.070
C13	0.3750(3)	0.0670(2)	1.0404(2)	0.0587(7)
H13	0.3692	0.0113	1.0888	0.070
C14	0.4892(3)	0.1151(2)	1.01896(19)	0.0554(6)
H14	0.5615	0.0931	1.0532	0.067
C15	0.4976(2)	0.19657(18)	0.94629(18)	0.0439(5)
H15	0.5756	0.2299	0.9325	0.053
C16	0.3215(2)	0.16771(17)	0.6921(2)	0.0487(6)
H16A	0.3309	0.1369	0.6274	0.073
H16B	0.2407	0.2049	0.6975	0.073
H16C	0.3265	0.1071	0.7392	0.073
C17	0.4185(2)	0.34362(16)	0.62942(17)	0.0461(5)
H17A	0.3300	0.3620	0.6183	0.055
H17B	0.4604	0.4127	0.6515	0.055
C18	0.4763(3)	0.3076(2)	0.5346(2)	0.0700(9)
H18A	0.5663	0.2999	0.5425	0.105
H18B	0.4588	0.3640	0.4855	0.105
H18C	0.4410	0.2357	0.5149	0.105

Table 2: Anistropic Displacement Factors:

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S1	0.0620(4)	0.0564(4)	0.0674(4)	0.0068(3)	-0.0130(3)	0.0141(3)
C1	0.0435(13)	0.0489(12)	0.0590(15)	-0.0011(11)	-0.0008(11)	0.0120(10)
C2	0.0366(11)	0.0353(10)	0.0505(13)	-0.0031(9)	0.0007(10)	0.0041(8)
C3	0.0386(11)	0.0316(10)	0.0486(13)	-0.0040(9)	0.0062(10)	0.0038(9)
C4	0.0385(13)	0.0498(13)	0.0640(16)	-0.0032(11)	0.0120(11)	-0.0007(10)
C5	0.0518(15)	0.0442(12)	0.0795(19)	0.0116(13)	0.0113(14)	-0.0063(10)
C6	0.0474(13)	0.0254(9)	0.0646(15)	0.0003(10)	0.0028(11)	-0.0051(8)
N1	0.0402(10)	0.0237(7)	0.0443(10)	0.0002(7)	0.0030(8)	0.0009(7)
C7	0.0453(12)	0.0235(8)	0.0320(10)	-0.0008(7)	-0.0007(9)	0.0010(8)
O7	0.0504(9)	0.0218(6)	0.0516(9)	-0.0041(6)	-0.0068(7)	0.0025(6)
C8	0.0407(11)	0.0231(8)	0.0454(12)	-0.0010(8)	-0.0088(9)	0.0012(8)
C9	0.0342(10)	0.0254(8)	0.0499(12)	-0.0049(9)	-0.0016(10)	0.0004(7)
O9	0.0455(9)	0.0301(7)	0.0749(12)	-0.0018(8)	0.0024(8)	0.0075(6)
C10	0.0430(12)	0.0265(9)	0.0464(12)	-0.0072(8)	0.0057(9)	-0.0008(8)
C11	0.0416(12)	0.0417(12)	0.0626(15)	-0.0089(11)	0.0082(11)	-0.0071(10)
C12	0.0622(16)	0.0446(13)	0.0679(18)	-0.0093(12)	0.0247(14)	-0.0168(12)
C13	0.0805(19)	0.0376(12)	0.0579(15)	0.0056(11)	0.0231(15)	0.0025(11)
C14	0.0638(16)	0.0512(14)	0.0513(15)	0.0054(11)	0.0089(12)	0.0118(11)
C15	0.0399(12)	0.0401(11)	0.0517(14)	0.0002(10)	0.0067(10)	0.0037(9)
C16	0.0471(13)	0.0318(10)	0.0671(16)	-0.0056(10)	-0.0158(12)	-0.0011(9)
C17	0.0620(14)	0.0262(10)	0.0501(13)	-0.0003(9)	-0.0161(12)	0.0050(9)
C18	0.126(3)	0.0402(13)	0.0441(14)	0.0017(11)	-0.0070(16)	0.0044(15)