Supporting information

New and Efficient Synthesis of Azabicyclo[4.4.0]alkane Amino Acids by Rh-Catalyzed Cyclohydrocarbonylation

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General Method. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-600 (600 MHz ^{1}H, 150 MHz ^{13}C), Varian Inova-400 (400 MHz ^{1}H, 100 MHz ^{13}C),Gemini-2300 (300 MHz ^{1}H, 75 MHz ^{13}C), a General Electric QE-300 (300 MHz ^{1}H, 75 MHz ^{13}C) or a Bruker AC-250 (250 MHz ^{1}H, 62.5 MHz ^{13}C) spectrometer in deuterated solvents using residual protons ($CHCl_3$: 7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as the internal reference unless otherwise stated. NMR solvents were dried over anhydrous K_2CO_3 or by passing through a short column of activated alumina. Chemical shifts (δ) are given in parts per million down field from tetramethylsilane (TMS). Infrared spectra were recorded on a Mattson Galaxy Series-3000 FTIR spectrometer using samples as neat oils or as KBr disks. Analytical gas chromatography was performed with a Hewlett-Packard 5890 Series II gas chromatograph (FID) with a Hewlett-Packard HP 3396A integrator using either a 15 m J&W DB-1, a 30 m J&W DB-17, or a 25 m 3% OV-101 capillary column. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. High resolution mass spectrometric analyses were conducted at the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign. TLC analyses were performed on Merck aluminum backed Kieselgel 60 F_{254} with visualization by 5 % solution of phosphomolybdic acid in ethanol or 0.1 % solution of ninhydrine in ethanol with a drop of HBr. The HPLC analysis was carried out on a Waters 600E multisolvent delivery system connected to a Waters MILLENNIUM workstation using a reversed phase C18 column using acetonitrile/water as eluant.

Materials. All solvents used as reaction media were distilled under nitrogen immediately before use: Ether, THF, and toluene were distilled from Na/benzophenone ketyl, and CH_2Cl_2 was distilled from CaH_2. Hydrogen and carbon monoxide were purchased from Praxair Co. $Rh(acac)(CO)_2$, was a gift from Mitsubishi Chemical Corporation and used as received. Solvents for extraction and chromatography were reagent grade and used as received. Chemicals and reagents were purchased form Aldrich, Sigma, or Fisher Scientific, and were used without further purification unless otherwise specified. Silica gel used for chromatography, MN-Kieselgel 60, was purchased from Brinkman Instruments Inc.

General procedure for preparation of dipeptide substrates

Dipeptide substrates **1** were prepared according to the standard peptide coupling method using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazol (HOBt). A general procedure is as follows: To a solution of (*S*)- or (*R*)-allylglycine methyl ester hydrochloride (0.30 mmol), *N*-protected amino acid (0.30 mmol), HOBt (54 mg, 0.40 mmol), and triethylamine (43 μL, 31 mg, 0.30 mmol) in CH_2Cl_2 (1 mL) was added EDC (65 mg, 0.339 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was poured into EtOAc (20 mL) and then washed with $NaHCO_3$ (0.1*N*, 20 mL) and sat. NH_4Cl. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified on a silica gel column (hexane / EtOAc) to afford the corresponding *N*-protected dipeptide methyl ester.

Methyl *N*-*tert*-butoxycarbonyl-(*S*)-serinyl-(*S*)-allylglycinate (*S*,*S*-1a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38(s, 9H), 2.48(m, 2H), 3.63 (m, 1H), 3.67 (s, 3H), 3.91 (m, 1H), 4.16 (m, 1H), 4.57 (dd, J= 12.8; 6.8 Hz, 1H), 5.06 (m, 2H), 5.63 (m, 2H), 7.24 (br, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 28.15, 35.92, 51.88, 52.37, 55.06, 62.73, 80.25, 119.12, 131.96, 155.90, 171.89, 174.22.

Methyl *N*-*tert*-butoxycarbonyl-(*S*)-serinyl-(*R*)-allylglycinate (*S*,*R*-1a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38(s, 9H), 2.48(m, 2H), 3.64 (m, 1H), 3.67 (s, 3H), 3.95 (m, 1H), 4.16 (m, 1H), 4.58 (dd, J= 12.8; 6.8 Hz, 1H), 5.08 (m, 2H), 5.62 (dddd, J= 17.2;10; 7.2; 7.2 Hz 1H), 5.73 (d, J= 6.0 Hz, 1H), 7.19 (br, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 28.15, 35.96, 51.67, 52.36, 55.47, 62.74, 80.29, 119.21, 131.93, 155.93, 171.10, 171.95.

Methyl (β-*tert*-butoxycarbonyl)-*N*-*tert*-butoxycarbonyl-(*S*)-alanyl-(*S*)-allylglycinate (*S*,*S*-1b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.45 (s, 9H), 2.44-2.65 (m, 2H), 3.49 (m, 2H), 3.74 (s, 3H), 4.18 (m, 1H), 4.62 (m, 1H), 5.10-5.14 (m, 3H), 5.61-5.75 (m, 2H), 7.11 (bs, 1H). HRMS (FAB) *m/z* calcd for $C_{19}H_{33}N_3O_7$•H^+ 416.2397; found 416.2396 (Δ = - 0.1 ppm).

Methyl *N*-(benzyloxycarbonyl)-*S*-triphenylmethyl-(*S*)-cysteinyl-(*S*)-allylglycinate (*S*,*S*-1c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (m, 1H), 2.52 (m, 1H), 2.58 (dd, J=13.0; 5.6 Hz, 1H), 2.74 (dd, J=13.0; 7.6 Hz, 1H), 3.66 (s, 3H), 3.85 (m, 1H), 4.57 (dd, J=13.0; 6.0 Hz, 1H), 5.05 (m, 4H), 5.34 (d, J=7.6 Hz, 1H), 5.61 (m, 1H), 6.58 (d, J= 6.4 Hz 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 33.61, 36.05, 51.67, 52.08, 53.29, 66.82, 67.03, 80.29, 119.01, 126.27, 127.79, 127.86, 127.94, 128.27, 129.36, 131.77, 135.96, 144.20, 155.65, 169.68, 171.25.

Methyl *S*-triphenylmethylthio-*N*-phthalyl-(*S*)-cysteinyl-(*S*)-allylglycinate (*S*,*S*-1d): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.40 - 2.61 (m, 2H), 2.87 (m, 1H), 3.52 (m, 1H), 3.67 (s, 3H), 3.85 (bs, 1H), 4.58 (m, 1H), 5.06 (m, 2H), 5.64 (m, 1H), 6.20 (m, 1H) 7.16 - 7.42 (m, 15H), 7.70 - 7.84 (m, 4H).

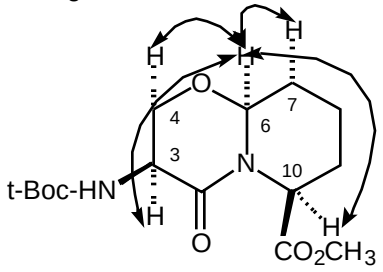
General procedure for cyclohydrocarbonylation of dipeptide

To a 10 mL round-bottomed reaction flask were placed $Rh(acac)(CO)_2$ (0.5 mg, 0.002 mmol, 2 mol%) and BIPHEPHOS (3 mg, 0.004 mmol, 2 mol%). The atmosphere of the reaction flask was replaced with nitrogen, followed by the addition of toluene (1 mL). The resulting solution was allowed to stir until it became homogeneous. In another 10 mL round-bottomed flask was prepared a solution of dipeptide (0.100 mmol) in 2

mL of toluene (or another solvent) under nitrogen. The substrate solution was transferred to the reaction flask via syringe under nitrogen. The reaction flask was placed in a 300 mL stainless steel autoclave, and the autoclave was flushed with CO several times. Then, the autoclave was filled with 2 atm of CO and 2 atm of H_2. The autoclave was placed in an oil bath that was maintained at 60 - 65 °C and the reaction mixture was magnetically stirred for 20 h at this temperature. Then, the autoclave was cooled to room temperature and pressure was slowly and carefully released. The reaction mixture was evaporated to give viscous oil. The crude oily product was purified by flash chromatography on silica gel using hexane/EtOAc as eluant to afford the desired bicyclo[4.4.0]alkane amino acid ester.

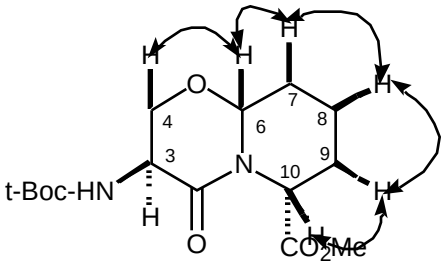
Methyl (3*S*,6*S*,10*S*)-1-aza-2-oxo-3-*tert*-butoxycarbonylamino-5-oxabicyclo[4.4.0]deca-ne-10-carboxylate (*S*,*S*,*S*-5a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.52 (m, 1H), 1.71 (m, 2H), 1.92 (m, 3H), 3.68 (s, 3H), 3.79 (dd, J = 10.2; 7.0 Hz, 1H), 4.16 (dd, J = 10.2; 6.2 Hz, 1H), 4.41-4.43 (m, 2H), 4.93 (dd, J = 8.4; 4.4 Hz, 1H), 5.36 (d, J=6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.46, 24.37, 28.01, 28.18, 49.78, 52.36, 53.97, 67.04, 80.01, 82.68, 155.42, 168.43, 171.51. . HRMS (FAB) *m/z* calcd for $C_{15}H_{24}N_2O_6$•H^+: 329.1713. Found: 329.1713 (Δ = 0.0 ppm). HPLC analysis showed only single peak and no trace of other diastereomers was observed.

Singnicant ROESY correlation



Methyl (3*S*,6*R*,10R)-1-aza-2-oxo-3-*tert*-butoxycarbonylamino-5-oxabicyclo[4.4.0]decane-10-carboxylate (*S*,*R*,*R*-5a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 2H); 1.40 (s, 9H); 1.63 (m, 1H); 1.73 (m, 1H); 1.94 (m, 1H); 2.17 (m, 1H); 3.69 (s, 3H), 4.00 (m, 2H), 4.25 (m, 1H), 4.91 (dd, J = 10.2, 3.4 Hz, 1H), 5.23 (d, J=7.2 Hz, 1H), 5.33 (d, J=5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) _ 19.07, 26.08, 28.25, 31.38, 50.88, 52.17, 52.51, 68.23, 80.14, 85.14, 155.24, 166.54, 171.10 . HRMS (FAB) *m/z* calcd for $C_{15}H_{24}N_2O_6$•H^+: 329.1713. Found: 329.1713 (Δ = 0.0 ppm). HPLC analysis showed only single peak and no trace of other diastereomers was observed.

Singnicant NOE correlation



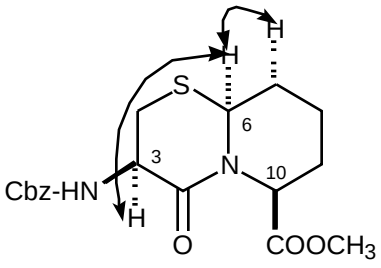
Methyl (3*S*,6*S*,10*S*)-1,5-diaza-2-oxo-3-(*tert*-butoxycarbonylamino)-5-(*tert*-butoxycarbonyl)-bicyclo[4.4.0]-decane-10-carboxylate [(*S*,*S*,*S*-5b)]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.49 (s, 3H), 1.65-2.02(m, 6H),

3.03 (t, J=12 Hz, 1H), 3.71 (s, 3H), 3.74 (m, 1H), 4.01 (ddd, J=10.8, 4.8, 4.8 Hz, 1H), 4.60 (br, 1H), 5.30 (br, 1H 5.47(br 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.50, 24.54, 28.26, 29.58, 41.65, 50.34, 52.22, 59.82, 68.46, 79.83, 81.75, 153.20, 155.43, 167.78, 169.53. HRMS (FAB) *m/z* calcd for $C_{20}H_{33}N_3O_7$•H^+: 428.2397. Found: 428.2398 (_ = 0.2 ppm). HPLC analysis showed only single peak and no trace of other diastereomers was observed.

Methyl (3*S*,6*S*,10*S*)-1-aza-2-oxo-3-benzyloxycarbonylamino-5-thiabicyclo[4.4.0]decane-10-carboxylate [(*S*,*S*,*S*)-5c]: The cyclohydrocarbonylation of (*S*)-*N*-carbobenzyloxy-*S*-triphenyl-methylcysteinyl-(*S*)-allylglycine methyl ester (**1c**) (80 mg, 0.131 mmol) was carried out in MeOH (3 mL) under the standard conditions described above except for the solvent, followed by purification on a silica gel column using hexane/EtOAc to give of (*S*)-*N*-carbobenzyloxy-*S*-triphenylmethylcysteinyl-(*S*)-(4,4-dimethoxybutyl)glycine methyl ester (**7**) (77 mg, 86% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (m, 2H), 1.54 (m, 2H), 1.81 (m, 2H), 2.53 (dd, J = 5.2, 13.1 Hz, 1H), 2.81 (dd, J = 7.1, 13.1 Hz, 1H), 3.25 (s, 6H), 3.68 (s, 3H), 3.85 (bs, 1H), 4.29 (t, J = 5.6 Hz, 1H), 4.50 (dd, J = 7.3, 13.0 Hz, 1H), 5.07 (s, 2H), 5.12 (m, 1H), 6.38 (m, 1H) 7.16 - 7.42 (m, 20H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.2, 31.9, 32.0, 33.9, 52.1, 52.3, 52.6, 52.8, 53.9, 67.1, 67.3, 104.1, 126.9, 127.9, 128.0, 128.2, 128.5, 129.5, 136.0, 144.3, 169.7, 170.4, 172.1.

To a solution of **7** (40 mg, 0.058 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (1 μL, 1.5 mg, 0.010 mmol) at room temperature and stirred for 30 min. The reaction mixture was poured into saturated $NaHCO_3$ (3 mL) and extracted with EtOAc (5 mL × 3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified on a silica gel column (EtOAc / Hex = 5 / 1 to 2 / 1) to afford **(*S*,*S*,*S*)-5c** (19.7 mg, 0.052 mmol, 89 %) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (m, 1H); 1.67 (m, 1H); 1.75 (m, 1H); 1.89 (m, 1H); 1.99 (m, 1H); 2.21 (m, 1H); 2.69 (dd, J = 12.0, 10.5 Hz, 1H), 3.50 (dd, J = 10.5, 6.0 Hz, 1H), 3.70 (s, 3H), 4.69 (ddd, J = 12.0, 6.0, 6.0 Hz, 1H) 4.80 (dd, J = 7.2, 3.6 Hz, 1H), 5.09 (m, 3H), 6.13 (d, 1H, J = 6.0 Hz), 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.19, 24.60, 27.75, 28.98, 51.48, 52.42, 53.06, 53.45, 66.86, 127.90, 128.04, 128.42, 136.16, 155.52, 170.88, 171.51. HRMS (FAB) *m/z* calcd for $C_{18}H_{22}N_2O_5S$•H^+: 379.1327. Found: 379.1328 (Δ = 0.2 ppm). HPLC analysis showed only single peak and no trace of other diastereomers was observed.

Singnicant ROESY correlation



Methyl (3*R*,6*R*,10*S*)-1-aza-2-oxo-3-phthalylimido-5-thiabicyclo[4.4.0]decane-10-carboxylate [(*R*,*R*,*S*)-8]: White solid; 60% yield for two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (bs, 1H), 1.67 (m, 1H), 1.78 (m, 1H), 1.93 (m, 1H, 2.20 (m, 1H), 2.30 (m, 1H), 2.78 (dd, J = 5.7, 13.2 Hz, 1H), 3.81 (dt, J = 11.4, 13.2 Hz, 1H), 4.62 (m, 1H) 5.15 (dd, J = 5.7, 11.4 Hz, 1H), 5.68 (m, 1H), 7.71-7.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 24.5, 25.9, 33.8, 50.9, 52.5, 55.4, 56.1, 123.6, 131.9, 134.2, 165.7, 167.6, 171.2. HRMS (FAB) *m/z* calcd for $C_{18}H_{18}N_2O_5S$•H^+: 375.1015. Found: 375.1015 (Δ = 0.0 ppm).

X-ray Crystallographic Analysis Data for (*S,S,S*)-5b and (*R,R,S*)-8

Table 1. Crystal data and structure refinement for Structure **(*S,S,*)*S*-5b**.

Empirical formula	C20 H33 N3 O7
Formula weight	427.49
Temperature	293(2) K
Wavelength	0.71073 ≈
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	
a = 8.848(3) ≈	α= 90∞.
b = 10.829(4) ≈	β= 90∞.
c = 24.104(8) ≈	γ = 90∞.
Volume	2309.6(13) ≈^{3}
Z 4	
Density (calculated)	1.229 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	920
Reflections collected	15096
Independent reflections	5438 [R(int) = 0.4679]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5438 / 0 / 287
Goodness-of-fit on F^2	0.558
Final R indices [I>2sigma(I)]	R1 = 0.0422, wR2 = 0.0877

Table 1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (≈^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x	y	z	U(eq)	
O(2)	-1401(10)	3454(7)	7942(3)	65(3)
O(6)	6578(9)	5849(8)	9069(3)	66(3)
O(4)	17(10)	4129(9)	10369(4)	64(3)
N(3)	4427(11)	4893(9)	8935(3)	59(4)
O(3)	221(10)	4774(9)	7527(3)	72(3)
O(1)	2862(9)	4079(9)	9851(3)	71(3)
N(2)	968(11)	3318(9)	9307(4)	44(3)
O(7)	4406(9)	6997(8)	8989(4)	78(4)
C(8)	403(12)	2515(13)	9755(6)	44(4)
C(11)	5061(18)	6050(17)	8986(6)	68(5)
C(4)	310(14)	2916(15)	8747(6)	67(5)
N(1)	832(13)	3814(10)	8350(4)	64(3)
C(2)	2824(15)	4787(11)	8891(6)	53(4)
C(9)	657(15)	3006(17)	10353(6)	74(6)
C(1)	2298(14)	3985(12)	9408(6)	53(4)
C(19)	-1750(13)	3037(11)	6955(4)	88(5)
C(5)	969(13)	1598(12)	8629(5)	72(4)
C(33)	2415(14)	4213(12)	8331(5)	90(5)
C(12)	7589(15)	6927(14)	9126(6)	75(4)
O(5)	1222(11)	2406(9)	10718(4)	90(4)
C(13)	7554(13)	7709(10)	8607(4)	77(4)
C(14)	7158(12)	7609(10)	9657(4)	78(5)
C(15)	9132(11)	6292(10)	9208(5)	112(6)
C(18)	-3236(12)	4675(11)	7448(4)	92(5)

C(16)	-71(16)	4063(15)	7897(6)	61(4)
C(6)	556(12)	714(12)	9107(5)	74(4)
C(10)	109(13)	4660(10)	10938(4)	93(5)
C(17)	-2536(14)	3365(13)	7474(6)	68(4)
C(20)	-3620(11)	2433(11)	7701(4)	82(5)
C(7)	1070(12)	1209(12)	9667(4)	67(4)

Table 1.3. Bond lengths [≈] and angles [∞]

O(2)-C(16)	1.353(14)
O(2)-C(17)	1.514(13)
O(6)-C(11)	1.374(15)
O(6)-C(12)	1.477(14)
O(4)-C(9)	1.342(17)
O(4)-C(10)	1.488(11)
N(3)-C(11)	1.378(16)
N(3)-C(2)	1.427(13)
O(3)-C(16)	1.207(14)
O(1)-C(1)	1.182(12)
N(2)-C(1)	1.402(13)
N(2)-C(8)	1.474(13)
N(2)-C(4)	1.532(14)
O(7)-C(11)	1.178(15)
C(8)-C(7)	1.547(15)
C(8)-C(9)	1.554(18)
C(4)-N(1)	1.441(13)
C(4)-C(5)	1.568(16)
N(1)-C(16)	1.379(14)
N(1)-C(33)	1.466(13)
C(2)-C(33)	1.529(14)
C(2)-C(1)	1.590(16)
C(9)-O(5)	1.202(15)
C(19)-C(17)	1.475(14)
C(5)-C(6)	1.543(13)
C(12)-C(13)	1.509(14)
C(12)-C(14)	1.526(14)
C(12)-C(15)	1.542(14)
C(18)-C(17)	1.549(13)
C(6)-C(7)	1.521(12)
C(17)-C(20)	1.496(14)
C(16)-O(2)-C(17)	123.3(11)
C(11)-O(6)-C(12)	118.7(12)
C(9)-O(4)-C(10)	110.7(11)
C(11)-N(3)-C(2)	119.0(12)
C(1)-N(2)-C(8)	117.4(11)
C(1)-N(2)-C(4)	128.3(10)
C(8)-N(2)-C(4)	110.4(10)
N(2)-C(8)-C(7)	108.0(10)
N(2)-C(8)-C(9)	115.4(11)
C(7)-C(8)-C(9)	112.6(12)
O(7)-C(11)-O(6)	128.2(17)
O(7)-C(11)-N(3)	126.2(16)
O(6)-C(11)-N(3)	105.5(14)
N(1)-C(4)-N(2)	105.7(11)
N(1)-C(4)-C(5)	111.9(12)
N(2)-C(4)-C(5)	106.1(10)
C(16)-N(1)-C(4)	118.2(12)
C(16)-N(1)-C(33)	118.1(12)

C(4)-N(1)-C(33)	121.7(10)
N(3)-C(2)-C(33)	109.5(11)
N(3)-C(2)-C(1)	106.1(10)
C(33)-C(2)-C(1)	113.6(11)
O(5)-C(9)-O(4)	130.1(16)
O(5)-C(9)-C(8)	123.6(17)
O(4)-C(9)-C(8)	106.0(13)
O(1)-C(1)-N(2)	123.8(13)
O(1)-C(1)-C(2)	122.5(13)
N(2)-C(1)-C(2)	113.0(12)
C(6)-C(5)-C(4)	109.9(11)
N(1)-C(33)-C(2)	108.6(10)
O(6)-C(12)-C(13)	110.7(11)
O(6)-C(12)-C(14)	108.0(10)
C(13)-C(12)-C(14)	114.7(12)
O(6)-C(12)-C(15)	101.3(11)
C(13)-C(12)-C(15)	112.0(11)
C(14)-C(12)-C(15)	109.2(12)
O(3)-C(16)-O(2)	123.8(14)
O(3)-C(16)-N(1)	125.9(15)
O(2)-C(16)-N(1)	110.2(13)
C(7)-C(6)-C(5)	111.9(11)
C(19)-C(17)-C(20)	116.8(13)
C(19)-C(17)-O(2)	109.5(10)
C(20)-C(17)-O(2)	101.3(11)
C(19)-C(17)-C(18)	112.0(12)
C(20)-C(17)-C(18)	112.1(11)
O(2)-C(17)-C(18)	103.7(10)
C(6)-C(7)-C(8)	109.2(11)

Symmetry transformations used to generate equivalent atoms:

Table 1.4. Anisotropic displacement parameters (≈^{2}x 10^3). The anisotropic displacement factor exponent takes the form: -2π^2[h^2 a*^{2}U^{11} + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
O(2)	57(7)	84(7)	55(6)	6(5)	-8(6)	-9(6)	
O(6)	45(5)	54(7)	99(7)	-6(6)	-4(6)	-10(6)	
O(4)	74(7)	70(8)	48(6)	-7(6)	-4(6)	-4(7)	
N(3)	54(8)	51(9)	70(8)	-1(6)	-3(7)	-16(7)	
O(3)	54(6)	90(9)	72(7)	21(6)	-8(6)	-18(6)	
O(1)	42(6)	121(9)	49(5)	10(7)	-19(5)	-22(6)	
N(2)	50(8)	48(8)	33(7)	3(6)	0(6)	-2(6)	
O(7)	45(7)	52(8)	136(8)	-10(7)	5(6)	-10(5)	
C(8)	26(8)	44(9)	61(10)	8(9)	-7(8)	-8(8)	
C(11)	57(12)	101(17)	47(9)	10(12)	16(10)	-7(13)	
C(4)	63(10)	91(14)	47(9)	40(9)	-6(10)	-39(11)	
N(1)	57(9)	86(10)	47(7)	4(7)	-11(7)	6(8)	
C(2)	37(9)	69(12)	54(9)	1(9)	-2(9)	-7(9)	
C(9)	44(13)	120(20)	56(13)	-24(14)	36(10)	-45(12)	
C(1)	25(9)	46(10)	90(12)	-5(11)	34(9)	7(8)	
C(19)	101(13)	122(14)	42(8)	-25(9)	-1(9)	-2(11)	
C(5)	63(11)	57(11)	95(12)	-24(10)	-14(9)	27(9)	
C(33)	49(11)	151(15)	69(11)	46(11)	-9(9)	-26(11)	
C(12)	38(10)	95(14)	92(12)	-11(11)	3(10)	-1(10)	
O(5)	116(8)	79(9)	74(8)	0(7)	-35(7)	8(7)	
C(13)	56(9)	74(11)	102(11)	21(9)	2(9)	-9(9)	
C(14)	69(10)	81(12)	85(10)	-25(10)	-19(9)	-9(10)	
C(15)	29(8)	119(16)	189(15)	-6(12)	-50(11)	-8(8)	

C(18)	79(11)	118(15)	80(10)	43(10)	-3(9)	17(10)
C(16)	36(10)	77(14)	69(13)	-17(10)	0(11)	10(10)
C(6)	58(9)	62(12)	102(12)	-20(11)	3(10)	6(8)
C(10)	135(13)	63(12)	79(10)	-20(9)	34(11)	-20(10)
C(17)	46(10)	71(12)	88(11)	-13(11)	-19(10)	5(9)
C(20)	62(10)	80(12)	104(12)	-1(9)	-34(9)	-8(10)
C(7)	70(10)	77(13)	54(9)	23(9)	5(8)	-6(10)

Table 1.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (≈^{2}x 10 ^{3}) .

x	y	z	U(eq)	
H(3)	4989	4245	8930	70
H(8)	-690(90)	2440(90)	9700(30)	52
H(4)	-800(100)	2900(90)	8760(40)	80
H(2)	2370(100)	5610(90)	8920(40)	64
H(19A)	-2438	3111	6649	133
H(19B)	-1392	2201	6978	133
H(19C)	-910	3583	6900	133
H(5A)	560	1284	8283	86
H(5B)	2059	1647	8592	86
H(33A)	2553	4814	8037	108
H(33B)	3065	3512	8256	108
H(13A)	6549	8019	8551	116
H(13B)	7848	7217	8294	116
H(13C)	8241	8389	8648	116
H(14A)	7252	7060	9967	117
H(14B)	6132	7892	9629	117
H(14C)	7818	8303	9707	117
H(15A)	9368	5805	8887	168
H(15B)	9091	5768	9529	168
H(15C)	9900	6908	9260	168
H(18A)	-3946	4715	7148	138
H(18B)	-2451	5272	7390	138
H(18C)	-3746	4849	7791	138
H(6A)	-530	594	9114	89
H(6B)	1025	-83	9042	89
H(10A)	1149	4792	11035	139
H(10B)	-342	4099	11198	139
H(10C)	-422	5433	10948	139
H(20A)	-3088	1683	7785	123
H(20B)	-4391	2267	7431	123
H(20C)	-4076	2750	8033	123
H(7A)	2165	1246	9679	81
H(7B)	731	663	9960	81

Table 2. Crystal data and structure refinement for ***(R,R,S)*-8**

Empirical formula	C18 H18 N2 O5 S
Formula weight	374.40
Temperature	293(2) K
Wavelength	0.71073 ≈
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	
a = 10.6300(11) ≈	α= 90∞.
b = 12.3905(13) ≈	β= 90∞.
c = 13.2483(14) ≈	γ = 90∞.
Volume	1744.9(3) ≈^{3}
Z 4	
Density (calculated)	1.425 Mg/m^3
Absorption coefficient	0.218 mm^{-1}
F(000)	784
Reflections collected	9821
Independent reflections	3552 [R(int) = 0.0248]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3552 / 0 / 245
Goodness-of-fit on F^2	0.937
Final R indices [I>2sigma(I)]	R1 = 0.0389, wR2 = 0.0927

Table 2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (≈^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x	y	z	U(eq)	
S(1)	10049(1)	4642(1)	8916(1)	67(1)
N(1)	7661(2)	4322(1)	9623(1)	51(1)
O(1)	6440(2)	2972(1)	9024(1)	66(1)
O(5)	8691(2)	1165(2)	9581(1)	68(1)
O(3)	5488(2)	6202(1)	10761(1)	70(1)
C(12)	8232(2)	1105(2)	8754(2)	50(1)
N(2)	8220(2)	1940(1)	8051(1)	50(1)
C(1)	7453(2)	3442(2)	9036(2)	49(1)
C(2)	8496(2)	3059(2)	8320(2)	52(1)
O(4)	7213(2)	2287(1)	6540(1)	75(1)
C(11)	7475(2)	1675(2)	7213(2)	54(1)
C(9)	6308(2)	5826(2)	10092(2)	61(1)
C(13)	7577(2)	193(2)	8272(2)	52(1)
C(16)	6209(3)	-1169(2)	7063(2)	75(1)
C(18)	7119(2)	529(2)	7354(2)	51(1)
C(4)	8877(2)	4800(2)	9881(2)	54(1)
C(17)	6438(3)	-134(2)	6737(2)	64(1)
C(7)	6976(3)	4379(2)	11387(2)	67(1)
C(8)	6642(2)	4655(2)	10300(2)	56(1)
C(5)	9265(2)	4444(2)	10929(2)	66(1)
C(14)	7363(3)	-847(2)	8608(2)	67(1)
C(3)	9839(2)	3228(2)	8685(2)	62(1)
O(2)	6704(2)	6341(2)	9397(2)	94(1)
C(10)	5036(3)	7289(2)	10557(2)	80(1)
C(6)	8262(3)	4780(2)	11687(2)	71(1)
C(15)	6658(3)	-1525(2)	7986(2)	78(1)

Table 2.3. Bond lengths [≈] and angles [∞].

S(1)-C(3)	1.794(2)
S(1)-C(4)	1.795(2)
N(1)-C(1)	1.357(3)
N(1)-C(4)	1.463(3)
N(1)-C(8)	1.466(3)
O(1)-C(1)	1.224(3)
O(5)-C(12)	1.202(3)
O(3)-C(9)	1.328(3)
O(3)-C(10)	1.455(3)
C(12)-N(2)	1.391(3)
C(12)-C(13)	1.473(3)
N(2)-C(11)	1.402(3)
N(2)-C(2)	1.462(3)
C(1)-C(2)	1.534(3)
C(2)-C(3)	1.521(3)
O(4)-C(11)	1.203(3)
C(11)-C(18)	1.481(3)
C(9)-O(2)	1.197(3)
C(9)-C(8)	1.518(3)
C(13)-C(18)	1.374(3)
C(13)-C(14)	1.382(3)
C(16)-C(17)	1.375(4)
C(16)-C(15)	1.384(4)
C(18)-C(17)	1.368(3)
C(4)-C(5)	1.514(3)
C(7)-C(6)	1.508(4)
C(7)-C(8)	1.523(4)
C(5)-C(6)	1.523(4)
C(14)-C(15)	1.395(4)
C(3)-S(1)-C(4)	98.14(12)
C(1)-N(1)-C(4)	127.05(18)
C(1)-N(1)-C(8)	117.19(18)
C(4)-N(1)-C(8)	113.35(17)
C(9)-O(3)-C(10)	114.7(2)
O(5)-C(12)-N(2)	124.7(2)
O(5)-C(12)-C(13)	129.3(2)
N(2)-C(12)-C(13)	106.01(18)
C(12)-N(2)-C(11)	111.17(19)
C(12)-N(2)-C(2)	122.68(18)
C(11)-N(2)-C(2)	121.87(19)
O(1)-C(1)-N(1)	122.2(2)
O(1)-C(1)-C(2)	118.7(2)
N(1)-C(1)-C(2)	119.02(18)
N(2)-C(2)-C(3)	113.3(2)
N(2)-C(2)-C(1)	107.41(18)
C(3)-C(2)-C(1)	116.06(19)
O(4)-C(11)-N(2)	124.7(2)
O(4)-C(11)-C(18)	129.7(2)
N(2)-C(11)-C(18)	105.56(19)
O(2)-C(9)-O(3)	123.9(2)
O(2)-C(9)-C(8)	124.5(2)
O(3)-C(9)-C(8)	111.6(2)
C(18)-C(13)-C(14)	120.6(2)
C(18)-C(13)-C(12)	108.54(19)
C(14)-C(13)-C(12)	130.8(2)
C(17)-C(16)-C(15)	121.0(3)
C(17)-C(18)-C(13)	122.3(2)

C(17)-C(18)-C(11)	129.5(2)
C(13)-C(18)-C(11)	108.19(19)
N(1)-C(4)-C(5)	109.7(2)
N(1)-C(4)-S(1)	113.77(16)
C(5)-C(4)-S(1)	115.60(18)
C(18)-C(17)-C(16)	117.7(2)
C(6)-C(7)-C(8)	112.8(2)
N(1)-C(8)-C(9)	109.3(2)
N(1)-C(8)-C(7)	110.1(2)
C(9)-C(8)-C(7)	116.2(2)
C(4)-C(5)-C(6)	109.5(2)
C(13)-C(14)-C(15)	117.4(2)
C(2)-C(3)-S(1)	107.79(16)
C(7)-C(6)-C(5)	111.8(2)
C(16)-C(15)-C(14)	121.0(3)

Symmetry transformations used to generate equivalent atoms:

Table 2.4. Anisotropic displacement parameters ($\approx^2$x 10^3). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
S(1)	55(1)	61(1)	86(1)	-3(1)	12(1)	-14(1)
N(1)	45(1)	47(1)	59(1)	-5(1)	0(1)	-1(1)
O(1)	47(1)	63(1)	88(1)	-19(1)	0(1)	-8(1)
O(5)	75(1)	70(1)	60(1)	9(1)	-19(1)	-6(1)
O(3)	65(1)	52(1)	94(1)	-10(1)	7(1)	8(1)
C(12)	47(1)	53(1)	49(1)	4(1)	-1(1)	7(1)
N(2)	56(1)	46(1)	47(1)	0(1)	-3(1)	2(1)
C(1)	44(1)	45(1)	60(1)	1(1)	-4(1)	-1(1)
C(2)	57(2)	45(1)	54(1)	3(1)	1(1)	-1(1)
O(4)	97(1)	71(1)	57(1)	17(1)	-16(1)	-15(1)
C(11)	61(2)	54(1)	46(1)	-1(1)	4(1)	-6(1)
C(9)	53(1)	60(2)	70(2)	-10(1)	-5(1)	10(1)
C(13)	49(1)	49(1)	57(1)	-3(1)	3(1)	9(1)
C(16)	81(2)	62(2)	81(2)	-15(1)	-10(2)	-7(2)
C(18)	54(1)	51(1)	46(1)	-4(1)	5(1)	1(1)
C(4)	49(1)	43(1)	71(2)	-7(1)	-2(1)	-5(1)
C(17)	70(2)	63(2)	59(1)	-7(1)	-4(1)	-6(1)
C(7)	75(2)	54(1)	71(2)	3(1)	14(1)	4(1)
C(8)	47(1)	49(1)	71(2)	-10(1)	1(1)	-2(1)
C(5)	56(2)	62(2)	79(2)	-5(1)	-16(1)	3(1)
C(14)	72(2)	53(1)	75(2)	7(1)	-5(1)	4(1)
C(3)	48(1)	60(1)	79(2)	-6(1)	6(1)	-3(1)
O(2)	114(2)	87(1)	82(1)	23(1)	19(1)	41(1)
C(10)	69(2)	54(2)	116(2)	-8(2)	-6(2)	13(1)
C(6)	84(2)	68(2)	62(1)	0(1)	-7(2)	6(2)
C(15)	83(2)	47(1)	103(2)	3(2)	-2(2)	-3(1)

Table 2.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\approx^2$x $10^{\ 3}$).

x	y	z	U(eq)	
H(2)	8410(20)	3480(20)	7699(18)	62
H(16)	5747	-1637	6659	90
H(4)	8730(20)	5580(20)	9931(17)	65

H(17)	6138	107	6116	77
H(7A)	6353	4695	11833	80
H(7B)	6946	3602	11473	80
H(8)	5900(20)	4220(20)	10122(18)	67
H(5A)	10064	4772	11106	79
H(5B)	9369	3666	10943	79
H(14)	7677	-1085	9224	80
H(3A)	10430	2982	8176	75
H(3B)	9984	2821	9299	75
H(10A)	4572	7293	9935	119
H(10B)	5740	7772	10502	119
H(10C)	4499	7520	11098	119
H(6A)	8477	4494	12347	86
H(6B)	8246	5561	11736	86
H(15)	6486	-2226	8195	93