Studies on C_{20}-Diterpenoid Alkaloids: Synthesis of the Hetidine Framework and its Application to the Synthesis of Dihydronavirine and the Atisine Skeleton

Amy M. Hamlin, David Lapointe, Kyle Owens, and Richmond Sarpong*

College of Chemistry, *University of California, Berkeley*

Berkeley, California 94720

rsarpong@berkeley.edu

SUPPORTING INFORMATION

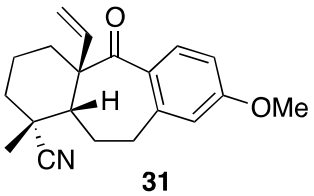
Table of Contents

General Experimental Details

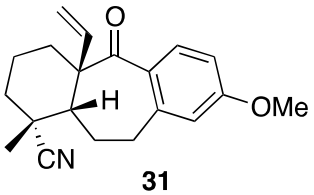
All reagents were obtained from commercial chemical suppliers and used without further purification unless otherwise noted. All reactions were performed in round-bottomed flasks or microwave vials sealed with rubber septa, under an atmosphere of nitrogen, and stirred with a Teflon^{TM}-coated magnetic stir bar unless otherwise noted. Temperatures above 23 °C were controlled by a temperature modulator. Microwave reactions were performed in a Biotage® Initiator Microwave Reactor equipped with an external IR sensor to monitor reaction temperature. Pre-dried tetrahydrofuran (THF), benzene, toluene, acetonitrile (MeCN), methanol (MeOH), and triethylamine (Et_3N), were degassed with argon for 60 min and passed through activated alumina columns. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride before use. Reactions were monitored by thin layer chromatography (TLC) using Silicycle Siliaplate^{TM} glass backed TLC plates (250 μm thickness, 60 Å porosity, F- 254 indicator) and visualized using UV (254 nm) and *p*-anisaldehyde stain or $KMnO_4$ stain. Volatile solvents were removed using a rotary evaporator under reduced pressure. Silica gel chromatography was performed using Sorbent Technologies 60 Å, 230 x 400 mesh silica gel (40-63 μm).

^{1}H NMR and ^{13}C NMR were obtained in $CDCl_3$ on 400, 500, or 600 MHz spectrometers with ^{13}C operating frequencies of 100, 126, or 151 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to residual chloroform (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is designated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), or m (multiplet). IR spectra were obtained as thin films on NaCl plates and reported in frequency of absorption (cm^{-1}). High-resolution mass spectral (HRMS) data was obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap) and the data was analyzed using Excalibur. High-resolution EI was obtained on an Autospec (magnetic sector) and the data was analyzed using MassLynx.

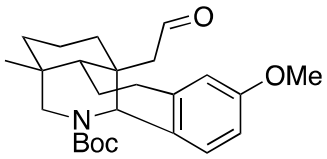
Procedures and supporting information for the synthesis of **14** and the X-ray crystallography data for **29**, **35** and **14** can be found in the previous communication ("Gallium(III)-Catalyzed Cycloisomerization Approach to the Diterpenoid Alkaloids: Construction of the Core Structure for the Hetidines and Hetisines" Hamlin, A. M.; Cortez, F. de J.; Lapointe, D.; Sarpong, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 4854. **DOI:** 10.1002/anie.201209030). Spectra that are included in this supporting information are supplemental to those reported in the previous communication. Spectra for the synthesis of dihydronavirine (**8**) and the atisine core (**63**) are also included in this supporting information.



31

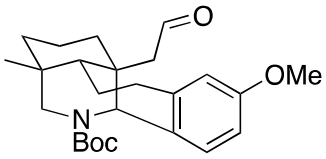


31


O
OMe
N
Boc

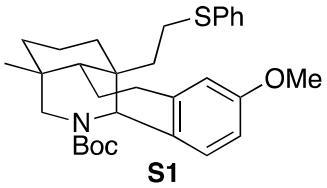
36

0.92
0.91
10.64
1.00
3.69
10.57
1.00
2.97
3.39
0.71
3.54
1.86
1.67
3.91
6.01
4.85
2.82
10.83
7.23
3.05
2.15
f1 (ppm)

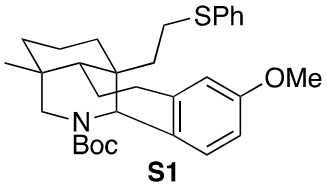

O
OMe
N
Boc

36

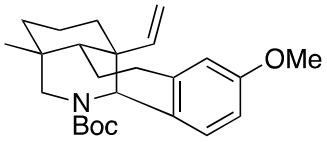
f1 (ppm)



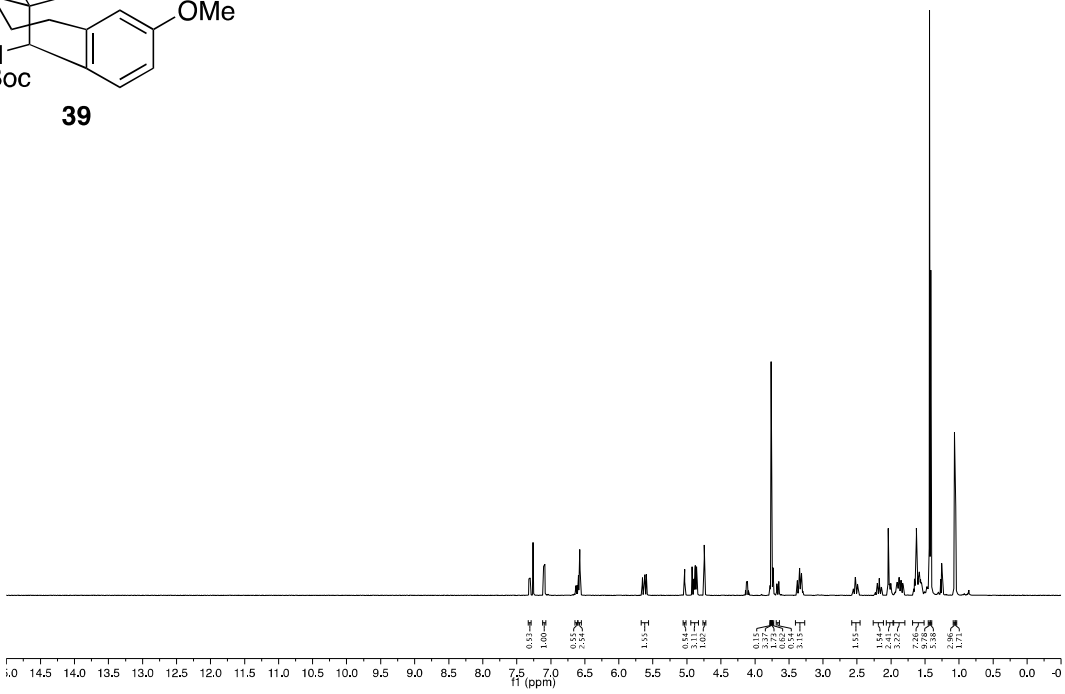
S1

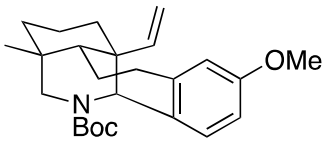


S1


OMe
N
Boc

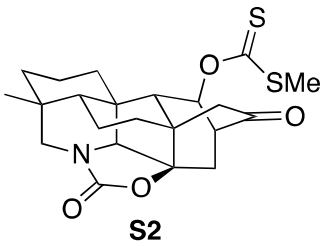
39


0.53
1.00
0.55
2.54
1.55
0.54
3.11
1.02
0.15
1.73
0.92
0.54
3.15
1.55
1.54
2.41
3.22
7.26
9.78
5.38
2.06
1.71
f1 (ppm)

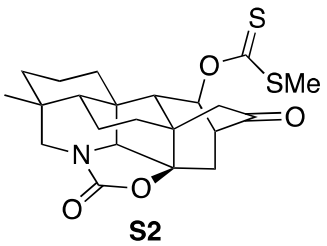

OMe
N
Boc

39

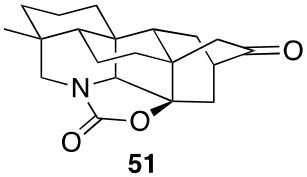
f1 (ppm)



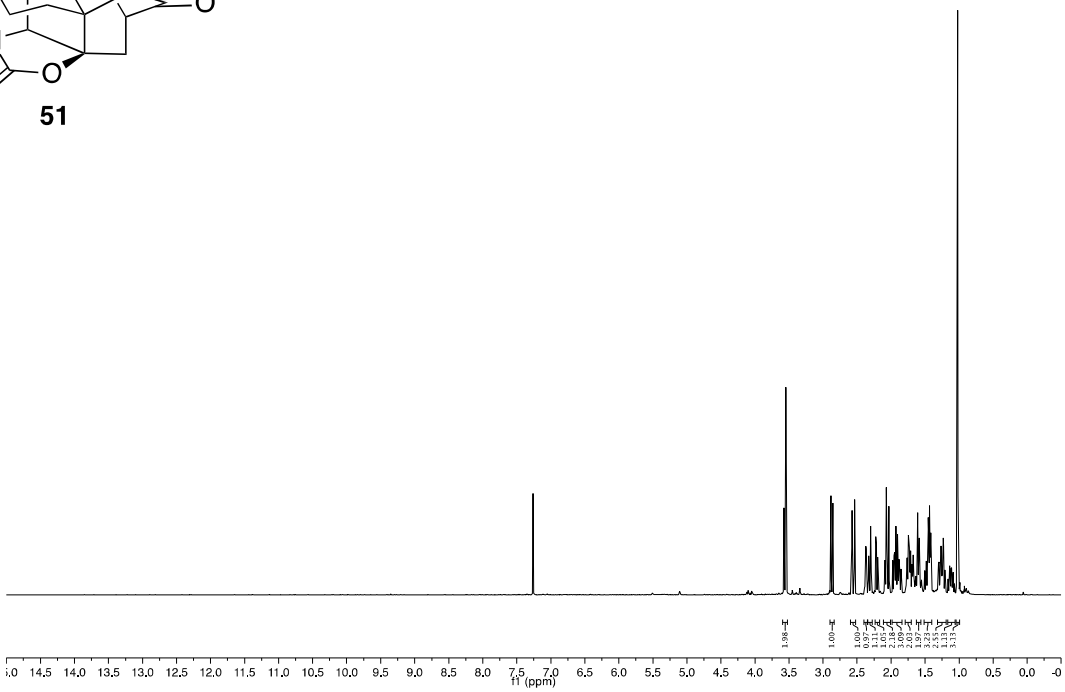
S2

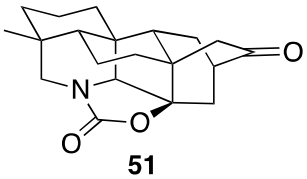


S2

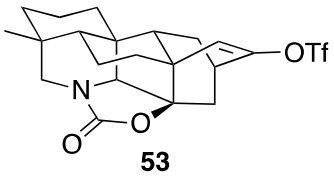


51

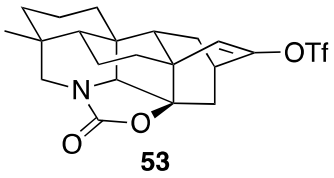




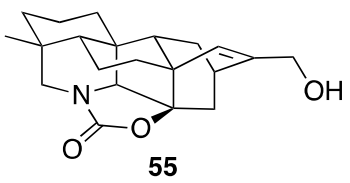
51



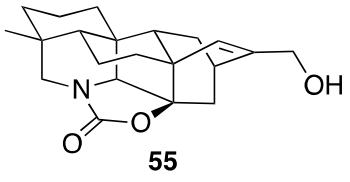
53



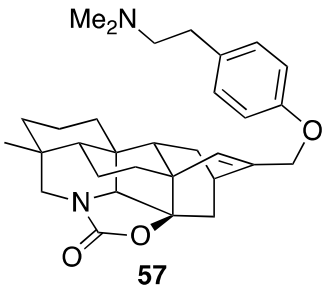
53



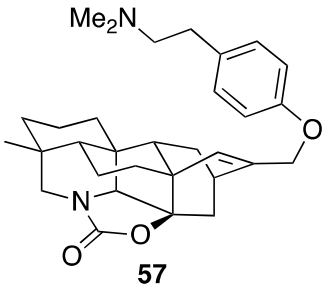
55



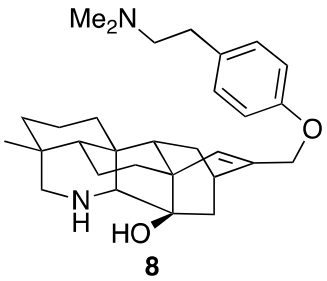
55



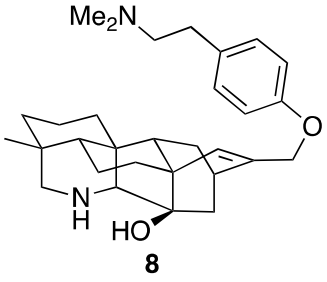
57



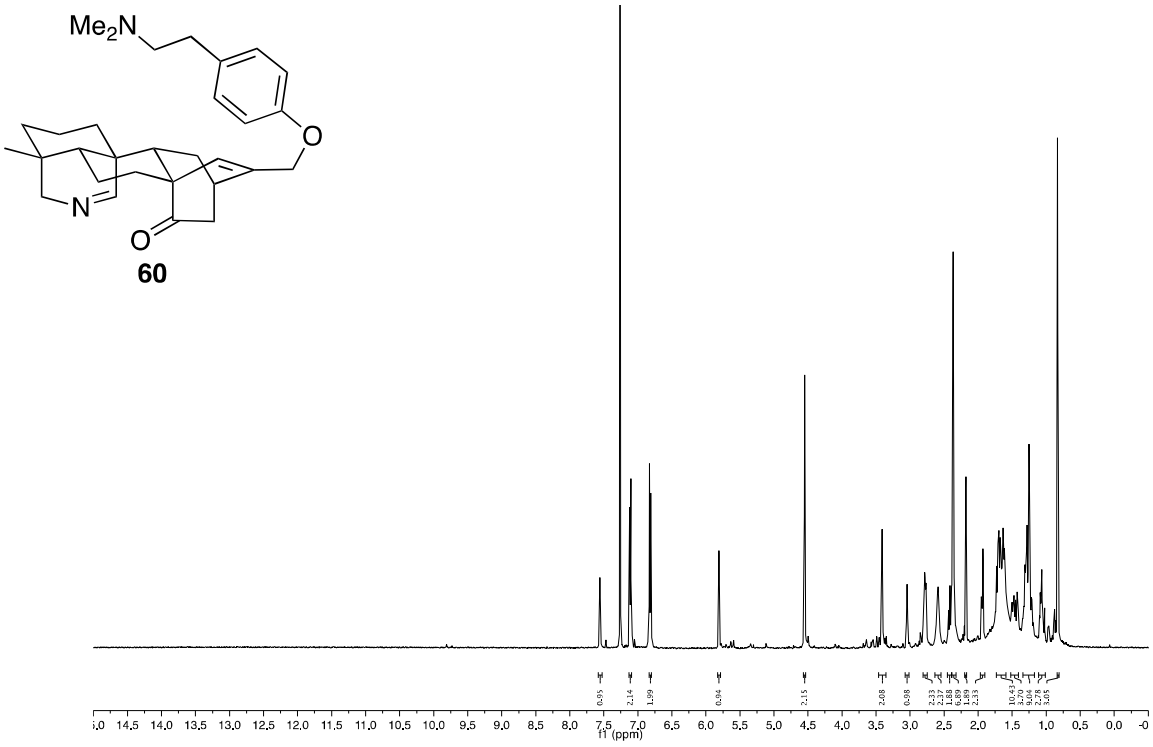
57

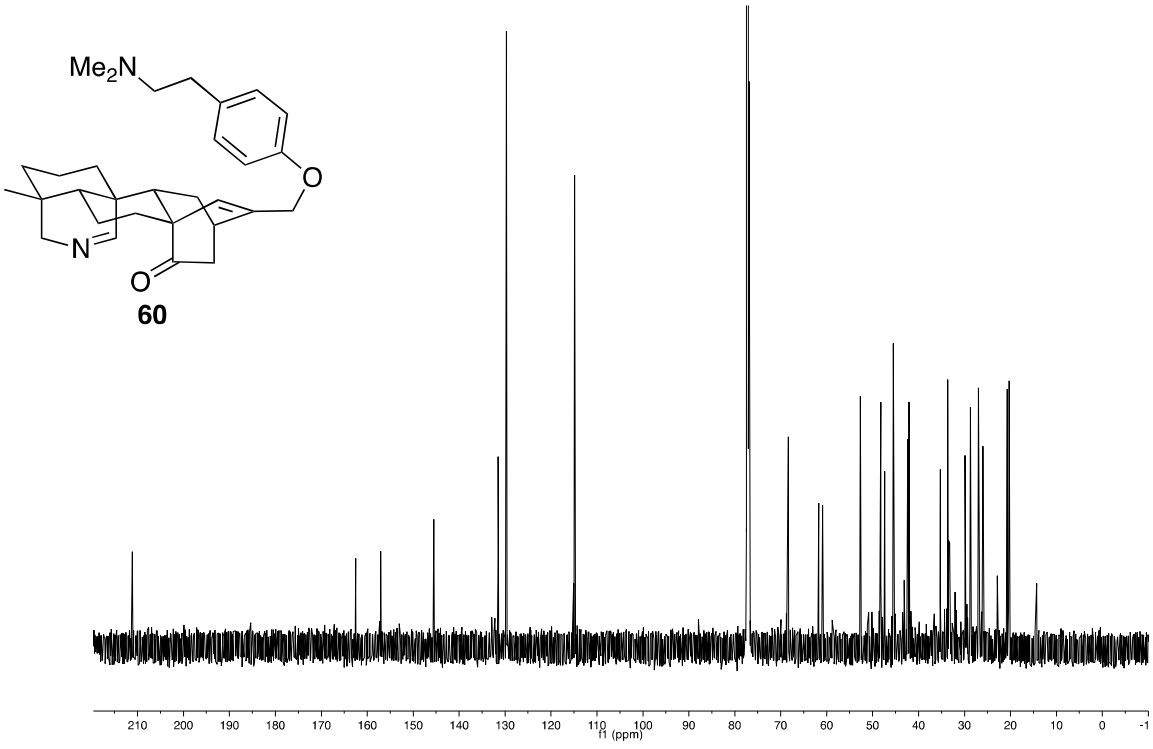


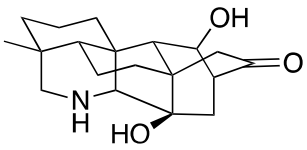
8



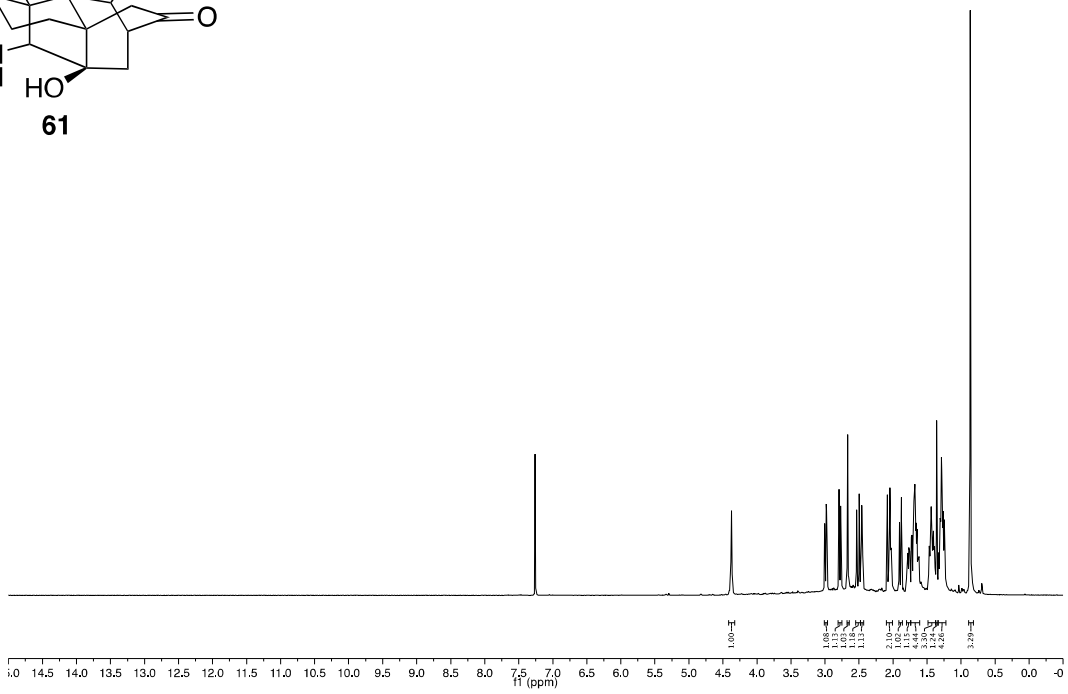
8

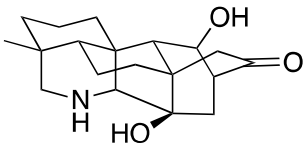

Me2N
O
N
O
60
f1 (ppm)


Me2N
O
N
O
60
f1 (ppm)


OH
O
N
H
HO

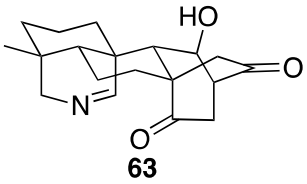
61


1.00
1.68
1.13
1.03
1.06
1.13
2.10
1.02
1.15
4.44
4.00
1.24
4.26
3.29
f1 (ppm)

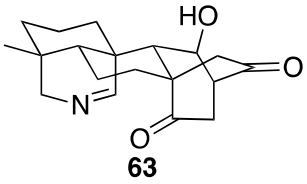

OH
O
N
H
HO

61

f1 (ppm)

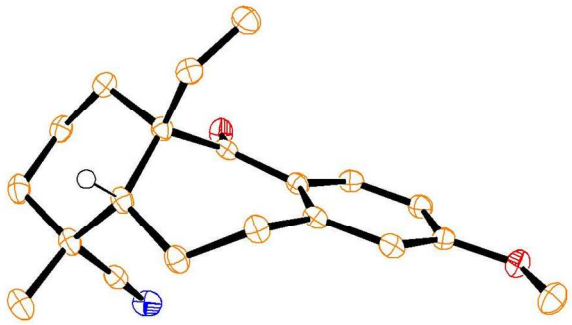


63



63

X-Ray Crystallography Data for 31



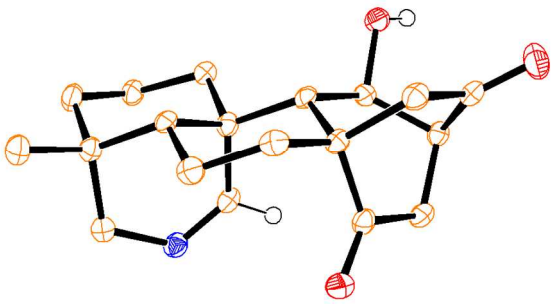
X-Ray Data and Crystal Refinement for 31

A colorless prism 0.150 x 0.100 x 0.100 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 98.3% complete to 67.000° in q. A total of 21234 reflections were collected covering the indices, -10<=*h*<=10, -20<=*k*<=20, -13<=*l*<=10. 2613 reflections were found to be symmetry independent, with an R_{int} of 0.0242. Indexing and unit cell refinement indicated a C-centered, monoclinic lattice. The space group was found to be C c (No. 9). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Empirical formula	C20 H23 N O2	
Formula weight	309.39	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C c	
Unit cell dimensions	a = 8.9580(4) Å	a = 90°.
	b = 17.1507(9) Å	b = 107.6180(10)°.
	c = 11.2099(5) Å	g = 90°.
Volume	1641.46(14) $Å^3$	
Z	4	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.632 mm^{-1}	
F(000)	664	
Crystal size	0.150 x 0.100 x 0.100 mm^3	
Crystal color/habit	colorless prism	
Theta range for data collection	5.158 to 68.160°.	
Index ranges	-10<=h<=10, -20<=k<=20, -13<=l<=10	
Reflections collected	21234	
Independent reflections	2613 [R(int) = 0.0242]	
Completeness to theta = 67.000°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.864 and 0.810	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2613 / 2 / 210
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0228, wR2 = 0.0615
R indices (all data)	R1 = 0.0229, wR2 = 0.0616
Absolute structure parameter	0.09(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.178 and -0.125 e.$Å^{-3}$

X-Ray Crystallography Data for 63



X-Ray Data and Crystal Refinement for 63

A colorless needle 0.050 x 0.020 x 0.010 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 100.0% complete to 67.000° in q. A total of 22824 reflections were collected covering the indices, -13<=*h*<=13, -8<=*k*<=8, -13<=*l*<=13. 3360 reflections were found to be symmetry independent, with an R_{int} of 0.0744. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Empirical formula	C21 H31 N O4	
Formula weight	361.47	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.9297(3) Å	a = 90°.
	b = 7.3691(2) Å	b = 94.209(3)°.
	c = 11.4432(4) Å	g = 90°.
Volume	919.17(5) $Å^3$	
Z	2	
Density (calculated)	1.306 Mg/m^3	
Absorption coefficient	0.717 mm^{-1}	
F(000)	392	
Crystal size	0.050 x 0.020 x 0.010 mm^3	
Theta range for data collection	3.873 to 68.414°.	
Index ranges	-13<=h<=13, -8<=k<=8, -13<=l<=13	
Reflections collected	22824	
Independent reflections	3360 [R(int) = 0.0744]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.818	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3360 / 1 / 239
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0410, wR2 = 0.0791
R indices (all data)	R1 = 0.0549, wR2 = 0.0848
Absolute structure parameter	-0.16(18)
Extinction coefficient	n/a
Largest diff. peak and hole	0.206 and -0.159 e.$Å^{-3}$