Asymmetric Synthesis of Functionalized *trans*-2,6-Disubstituted Piperidines using *N*-Sulfinyl δ -Amino β -Ketoesters. Synthesis of (-)-Lasubine I.

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X-ray Structure of (2*S*,4*R*,6*R*)-(-)-7

Compound **7**, $C_{12}H_{17}NO$, crystallizes in the monoclinic space group $P2_1$ (systematic absences $0k0$: $k=\text{odd}$) with $a=7.344(3)\text{\AA}$, $b=7.054(3)\text{\AA}$, $c=11.485(5)\text{\AA}$, $\beta=112.473(8)^\circ$, $V=549.8(4)\text{\AA}^3$, $Z=2$ and $d_{\text{calc}}=1.155\text{ g/cm}^3$. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo- K_α radiation ($\lambda=0.71069\text{\AA}$) at a temperature of 143°K . Indexing was performed from a series of four 0.5° oscillation images with exposures of 20 seconds per frame. A hemisphere of data was collected using 60 second exposures and a crystal-to-detector distance of 35 mm. A total of 440 images were collected: one sweep was performed using ϕ -scans from -90° to $+90^\circ$ in 0.5° steps at $\omega = 0^\circ$ and $\chi = 0^\circ$ with a detector swing angle of -10° ; a second sweep was done using ω -scans from -20° to $+20^\circ$ in 0.5° steps at $\chi = -90^\circ$ and $\phi = 0^\circ$ with a detector swing angle of -10° . Oscillation images were processed using CrystalClear¹, producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the teXsan² program package for further processing and structure solution on a Silicon Graphics O2 computer. A total of 3362 reflections were measured over the ranges $6 \leq 2\theta \leq 50.68^\circ$, $-6 \leq h \leq 8$, $-8 \leq k \leq 7$, $-13 \leq l \leq 13$ yielding 1899 unique reflections ($R_{\text{int}} = 0.0228$). The intensity data were corrected for Lorentz and polarization effects and for absorption, using REQAB³ (minimum and maximum transmission 0.780, 1.000).

The structure was solved by direct methods (SIR92⁴). Refinement was by full-matrix least squares based on F^2 using SHELXL-93⁵. All reflections were used during refinement (F^2 's that were experimentally negative were replaced by $F^2 = 0$). The weighting scheme used was $w=1/[\sigma^2(F_o^2) +$

$0.0254P^2 + 0.1924P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically. Refinement converged to $R_1=0.0404$ and $wR_2=0.0852$ for 1764 reflections for which $F > 4\sigma(F)$ and $R_1=0.0453$, $wR_2=0.0875$ and $GOF = 1.106$ for all 1898 unique, non-zero reflections and 195 variables⁶. The maximum Δ/σ in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were +0.128 and -0.151 e/Å³.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 2. Anisotropic thermal parameters are in Table 3. Tables 4. and 5. list bond distances and bond angles. Figure 1. is an ORTEP⁷ representation of the molecule with 30% probability thermal ellipsoids displayed.

Figure 1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

References

1. CrystalClear: Rigaku Corporation, 1999.
2. teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).
3. REQAB4: R.A. Jacobsen, (1994). Private Communication.
4. SIR92: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidoro, G. (1994). *J. Appl. Cryst.*, **27**, 435.
5. SHELXL-93: Program for the Refinement of Crystal Structures, Sheldrick, G.M. (1993), University of Göttingen, Germany.
6. $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$
 $wR_2 = \{ \sum w (F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2 \}^{1/2}$
 $GOF = \{ \sum w (F_o^2 - F_c^2)^2 / (n - p) \}^{1/2}$
where n = the number of reflections and p = the number of parameters refined.
7. "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

Table 1. Summary of Structure Determination of Compound (-) 7

Formula:	$C_{12}H_{17}NO$
Formula weight:	191.27
Crystal class:	monoclinic
Space group:	$P2_1$ (#4)
Z	2
Cell constants:	
a	7.344(3) Å
b	7.054(3) Å
c	11.485(5) Å
β	112.473(8)°
V	549.8(4) Å ³
μ	0.73 cm ⁻¹
crystal size, mm	0.32 x 0.10 x 0.05
D_{calc}	1.155 g/cm ³
F(000)	208
Radiation:	Mo-K α ($\lambda=0.71069$ Å)
2 θ range	6 – 50.68 °
hkl collected:	-6 ≤ h ≤ 8; -8 ≤ k ≤ 7; -13 ≤ l ≤ 13
No. reflections measured:	3362
No. unique reflections:	1899 ($R_{int}=0.0228$)
No. observed reflections	1764 ($F>4\sigma$)
No. reflections used in refinement	1898
No. parameters	195
R indices ($F>4\sigma$)	$R_1=0.0404$ $wR_2=0.0852$
R indices (all data)	$R_1=0.0453$ $wR_2=0.0875$
GOF:	1.106
Final Difference Peaks, e/Å ³	+0.128, -0.151

Table 2. Refined Positional Parameters for Compound (-)-7

Atom	x	y	z	U _{eq} , Å ²
N1	0.5120(2)	0.6319(2)	0.8648(2)	0.0196(4)
C2	0.3159(3)	0.5677(3)	0.7786(2)	0.0188(4)
C3	0.2889(3)	0.3660(3)	0.8197(2)	0.0209(5)
C4	0.4524(3)	0.2331(3)	0.8197(2)	0.0217(4)
C5	0.6550(3)	0.3195(3)	0.8919(2)	0.0232(5)
C6	0.6717(3)	0.5206(3)	0.8498(2)	0.0211(5)
C7	0.2797(3)	0.5868(3)	0.6376(2)	0.0217(5)
C8	0.3673(4)	0.7337(4)	0.5971(2)	0.0323(5)
C9	0.3390(4)	0.7526(4)	0.4708(2)	0.0402(7)
C10	0.2193(4)	0.6283(4)	0.3834(2)	0.0402(6)
C11	0.1285(4)	0.4854(4)	0.4216(2)	0.0424(7)
C12	0.1577(4)	0.4644(4)	0.5475(2)	0.0335(6)
C13	0.8696(3)	0.6104(4)	0.9282(3)	0.0359(6)
O14	0.4359(2)	0.0531(2)	0.8729(2)	0.0317(4)
H1	0.524(3)	0.758(4)	0.850(2)	0.024(6)
H2	0.219(3)	0.652(3)	0.793(2)	0.013(5)
H3a	0.156(3)	0.317(3)	0.769(2)	0.025(6)
H3b	0.294(3)	0.376(3)	0.904(2)	0.017(5)
H4	0.436(3)	0.209(3)	0.731(2)	0.011(5)
H5a	0.758(3)	0.237(3)	0.879(2)	0.027(6)
H5b	0.677(3)	0.320(3)	0.979(2)	0.014(5)
H6	0.658(3)	0.521(3)	0.759(2)	0.019(5)
H8	0.444(4)	0.824(4)	0.660(3)	0.043(7)
H9	0.408(4)	0.862(5)	0.449(3)	0.055(8)
H10	0.201(4)	0.642(4)	0.299(3)	0.047(8)
H11	0.045(5)	0.389(5)	0.362(3)	0.060(9)
H12	0.092(4)	0.362(4)	0.573(2)	0.043(7)
H13a	0.890(3)	0.612(4)	1.016(2)	0.033(6)
H13b	0.870(4)	0.742(4)	0.898(3)	0.051(8)
H13c	0.978(4)	0.538(4)	0.913(3)	0.050(7)
H14	0.451(4)	0.067(4)	0.948(3)	0.046(8)
$U_{eq} = \frac{1}{3}[U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha]$				

Table 3. Refined Thermal Parameters (U's) for Compound (-) - 7

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	0.0255(9)	0.0119(9)	0.0213(9)	-0.0003(7)	0.0088(7)	-0.0016(7)
C2	0.0171(9)	0.0205(12)	0.0192(10)	0.0031(8)	0.0075(8)	0.0047(8)
C3	0.0220(11)	0.0237(12)	0.0172(10)	0.0019(8)	0.0078(9)	-0.0034(9)
C4	0.0345(12)	0.0130(11)	0.0177(10)	0.0022(8)	0.0100(8)	0.0000(8)
C5	0.0282(12)	0.0228(12)	0.0181(11)	0.0018(8)	0.0083(8)	0.0097(9)
C6	0.0212(11)	0.0221(12)	0.0201(10)	-0.0019(8)	0.0080(8)	-0.0010(8)
C7	0.0184(10)	0.0240(13)	0.0230(11)	0.0061(8)	0.0083(8)	0.0050(8)
C8	0.0348(13)	0.0317(14)	0.0287(12)	0.0089(10)	0.0102(10)	-0.0018(10)
C9	0.0355(14)	0.053(2)	0.0318(13)	0.0188(12)	0.0122(11)	0.0006(12)
C10	0.0368(14)	0.063(2)	0.0203(12)	0.0123(11)	0.0106(10)	0.0059(13)
C11	0.044(2)	0.055(2)	0.0235(12)	-0.0014(11)	0.0073(11)	-0.0088(12)
C12	0.0346(13)	0.039(2)	0.0251(12)	0.0031(10)	0.0093(10)	-0.0083(10)
C13	0.0274(12)	0.041(2)	0.038(2)	-0.0055(11)	0.0113(10)	-0.0058(11)
O14	0.0576(10)	0.0140(8)	0.0247(9)	0.0017(6)	0.0171(8)	-0.0006(7)

The form of the anisotropic displacement parameter is:
 $\exp[-2\pi^2(a^2U_{11}h^2+b^2U_{22}k^2+c^2U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$.

Table 4. Bond Distances in Compound (3), Å

N1-C2	1.472(3)	N1-C6	1.475(3)	N1-H1	0.92(3)
C2-C3	1.535(3)	C2-C7	1.543(3)	C2-H2	0.99(2)
C3-C4	1.523(3)	C3-H3a	0.99(2)	C3-H3b	0.96(2)
C4-O14	1.433(2)	C4-C5	1.527(3)	C4-H4	1.00(2)
C5-C6	1.519(3)	C5-H5a	1.01(2)	C5-H5b	0.95(2)
C6-C13	1.524(3)	C6-H6	1.00(2)	C7-C12	1.382(3)
C7-C8	1.391(3)	C8-C9	1.390(3)	C8-H8	0.97(3)
C9-C10	1.369(4)	C9-H9	1.00(3)	C10-C11	1.370(4)
C10-H10	0.93(3)	C11-C12	1.386(3)	C11-H11	0.99(3)
C12-H12	0.97(3)	C13-H13a	0.97(3)	C13-H13b	0.99(3)
C13-H13c	1.02(3)	O14-H14	0.83(3)		

Table 5. Bond Angles in Compound (3), °

C2-N1-C6	112.0(2)	C2-N1-H1	108.3(14)	C6-N1-H1	110.8(13)
N1-C2-C3	106.6(2)	N1-C2-C7	114.3(2)	C3-C2-C7	114.4(2)
N1-C2-H2	106.6(12)	C3-C2-H2	108.7(11)	C7-C2-H2	105.9(12)
C4-C3-C2	112.1(2)	C4-C3-H3a	112.5(13)	C2-C3-H3a	111.1(13)
C4-C3-H3b	108.8(12)	C2-C3-H3b	106.4(13)	H3a-C3-H3b	106(2)
O14-C4-C3	110.5(2)	O14-C4-C5	110.2(2)	C3-C4-C5	111.0(2)
O14-C4-H4	106.8(11)	C3-C4-H4	108.6(11)	C5-C4-H4	109.5(11)
C6-C5-C4	112.4(2)	C6-C5-H5a	109.7(13)	C4-C5-H5a	108.6(13)
C6-C5-H5b	109.1(13)	C4-C5-H5b	108.2(12)	H5a-C5-H5b	109(2)
N1-C6-C5	107.1(2)	N1-C6-C13	109.3(2)	C5-C6-C13	112.0(2)
N1-C6-H6	110.5(11)	C5-C6-H6	110.2(12)	C13-C6-H6	107.7(12)
C12-C7-C8	117.7(2)	C12-C7-C2	122.2(2)	C8-C7-C2	120.0(2)
C9-C8-C7	121.1(2)	C9-C8-H8	122(2)	C7-C8-H8	117(2)
C10-C9-C8	120.1(2)	C10-C9-H9	124(2)	C8-C9-H9	116(2)
C11-C10-C9	119.4(2)	C11-C10-H10	121(2)	C9-C10-H10	120(2)
C10-C11-C12	120.8(3)	C10-C11-H11	122(2)	C12-C11-H11	117(2)
C7-C12-C11	120.8(2)	C7-C12-H12	120(2)	C11-C12-H12	120(2)
C6-C13-H13a	110.9(14)	C6-C13-H13b	108(2)	H13a-C13-H13b	110(2)
C6-C13-H13c	109(2)	H13a-C13-H13c	112(2)	H13b-C13-H13c	108(2)
C4-O14-H14	110(2)				