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Crystal Structures and Absolute Configurations of Dexmedetomidine and Its Tosyl Derivative

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Abstract: X-ray diffraction data were used to determine the absolute configuration of dexmedetomidine, a new member of a class of drugs with 4-arylalkyl-1*H*-imidazole structure. When the anomalous effect of the parent compound proved to be too small for determination of the absolute configuration the tosyl derivative, with the same configuration, was synthesised and used as a reference. Stability of the stereogenic center was verified by HPLC technique. The absolute configuration of the compounds is S. Complete crystal structures are reported for both compounds. Co radiation was used for measurements.

Introduction

The crystal structures of medetomidine hydrochloride (Rec. INN), (±)-4-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole HCl (DOMITOR®; Orion Corporation FARMOS)[1] and detomidine hydrochloride, 4-(2,3-dimethylphenyl)methyl-1*H*-imidazole HCl (DOMOSEDAN®; Orion Corporation FARMOS)[2] have been reported in earlier papers. As was discovered recently, both these drugs are members of a family of molecules with 4-arylalkyl-1*H*-imidazole structure.[3] The medetomidine molecule possesses a stereogenic center and its dextro and levo enantiomers have been separated by resolution.[4] Pharmacological studies have shown that only the dextro enantiomer, dexmedetomidine hydrochloride (Rec. INN), is pharmacologically active.[5,6] Medetomidine is currently used as a veterinary psychopharmacological agent as it has strong sedative and analgesic properties; it has also been studied in human clinical trials.[7] Detomidine is in commercial use as an analgesic sedative for horse, cattle, and other large animals.[8,9] Dexmedetomidine [compound (1) in Scheme 1] human clinical trials are in progress.[10,11]

The aim of this study was to determine the absolute configuration of dexmedetomidine for molecular modelling and documentation purposes. The X-ray analysis of pure dexmedetomidine base crystal did not give reliable results because of the too small anomalous dispersion and we failed to obtain suitable crystals of dexmedetomidine salts. An indirect method, based on determining the absolute configuration of 1-tosyl dexmedetomidine, (+)-(S)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole [compound (2) in Scheme 1], was then successfully applied. The method relied on knowledge gained in earlier work that the stereogenic center of dexmedetomidine is highly stable. 1-Tosyl derivatives of racemic medetomidine and levomedetomidine were used as references in chromatographic studies to verify the stability of the stereogenic center during tosylation and detosylation. The two enantiomers of medetomidine and 1-tosyl-medetomidine were completely

separated by a direct HPLC method (Fig. 1) modified from earlier studies.[12] The tosylation and detosylation of dexmedetomidine, medetomidine, and levomedetomidine were carried out by trivial synthetic methods[13] (Scheme 1).

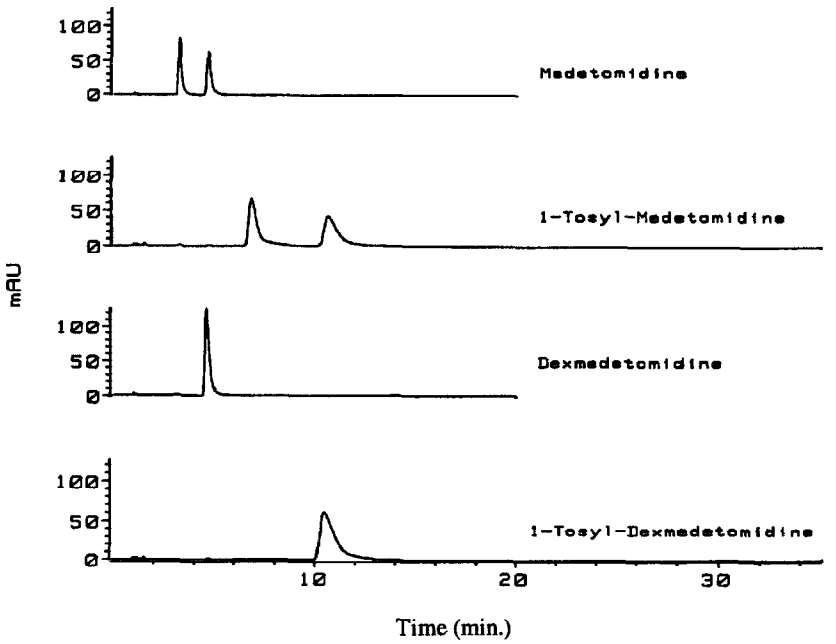
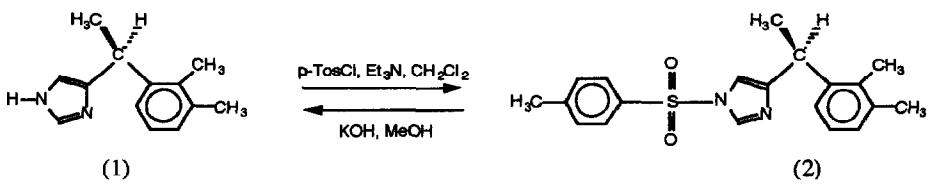


Figure 1. Separation of the two enantiomers of medetomidine base and 1-tosyl medetomidine base on Chiral AGP 4 x 100 mm stainless steel column. Mobile phase 30 mM potassium dihydrogen phosphate/disodium hydrogen phosphate buffer (pH 7.0) acetonitrile (800:200 v/v); flow-rate 0.8 ml/min; temperature, ambient.



Scheme 1. The tosylation and detosylation of dexmedetomidine.

X-Ray Crystal Structure Analysis

The structures of (+)-(S)-4-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole (Fig. 2) (recrystallized from water/isopropanol) and (+)-(S)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole (Fig. 3) (recrystallized from ethyl acetate) were established by single crystal X-ray analysis. For both compounds, cell dimensions and intensity data were measured with an Enraf-Nonius CAD-4 diffractometer up to $\theta = 75°$ (Co-K_α radiation). For crystal structure analysis the data were corrected for absorption, Lorentz, and polarization effects. All

calculations were carried out on a Microvax 3100 computer using SHELXS-86[14] for structure solutions and CRYSTALS[15] for refinements. Atomic scattering factors were taken from International Tables;[16] values for f' and f" and mass absorption coefficients for Co-radiation were taken from an article by D. Cromer[17] and added to the program. The coordinates of all non-hydrogen atoms were given by SHELXS-86. The hydrogen atoms were placed geometrically. The structures were refined by full-matrix least-squares with anisotropic temperature factors for all non-hydrogen atoms. For (1) the hydrogen atoms were refined with isotropic temperature factors and for (2) the hydrogen atoms were fixed at a distance of 1.00 Å, but not refined. Friedel opposites were not merged. Corrections for secondary extinction were applied,[18] and Chebychev weighting schemes[19] were used to give a final value of R_w = 0.0187 for (1) and R_w = 0.0340 for (2). Crystal data given in Table 1 correspond to the crystal structure solution procedure and all the tables were generated from these refinements.[20]

There are no significant differences between the bond lengths and angles of dexmedetomidine and its tosyl derivative and those of racemic medetomidine hydrochloride, its monohydrate[1] and detomidine,[2] which have been reported earlier. The bond lengths and angles of the imidazole rings are in agreement with those reported for other imidazole derivatives.[2] All rings in both compounds are planar. In dexmedetomidine the angle between the planes is 103.1°. The tosyl derivative crystallizes with two molecules in the asymmetric unit. The only notable difference between the molecules is in the torsional angles around the SO_2 group (see Table 9). In the tosyl derivative the angles between the imidazole ring and first phenyl ring (C1-C6) are 85.6° and 84.3°, respectively. The angles between the imidazole ring and second phenyl ring (C19-C24) are 75.1° and 70.9°, respectively. In dexmedetomidine there is one intermolecular hydrogen bond: it is from N(14) to N(12) with N···N 2.813(4) Å, N(14)-H 0.94(2) Å, H···N(12) 1.885(4) Å and N(14)-H···N(12) 169.2°.

Absolute configuration

Determination of absolute configuration by X-ray diffraction is based on an anomalous scattering of X-rays. At the very outset it was known that the method might not succeed for dexmedetomidine: the heaviest atoms in the structure are two nitrogens and the anomalous effect for them is very small. The determination of absolute configuration was first attempted using Cu radiation and then at low temperature (-30 °C) using Co radiation. Low temperature was used to minimize undesired effects such as thermal motion of the atoms. In both cases the result was the same. The anomalous effect proved to be too small and Flack's[21-23] x parameter gave unreliable values. Significantly the absorption correction (DIFABS)[24] greatly influenced the results. When only ψ-scan[25] absorption correction was applied and all data (1391 reflections) were used for refinement, the x parameter got the value -0.1(9) for Co data. When both ψ-scan and DIFABS absorption corrections were applied and 3σ was used as a cutoff limit, the x parameter got the value 0.1(3).

Altogether these results meant that there was not sufficient information in the data to determine reliably the absolute configuration of dexmedetomidine. The standard deviation of the x parameter was too high. As well, the marked effect of the absorption correction done by DIFABS led us to conclude that the result could not be reliable.

A tosyl derivative was then synthesized and its absolute configuration was easily determined. Absorption (only ψ-scan with correction factors min. 1.33 and max. 2.14), Lorentz, and polarization effects were corrected and all data (4801 reflections) were used for refinement. Refinement with the Chebychev weighting scheme with coefficients 2.29, 0.653, and -1.51 gave R_w = 0.048. The x parameter got a value of -0.01(2), so the result was unequivocal. The correct coordinate set for the tosyl derivative corresponds to S configuration. By HPLC it was proven that the configuration of dexmedetomidine did not change when the tosyl derivative was prepared. Hence, the absolute configuration of dexmedetomidine is also S.

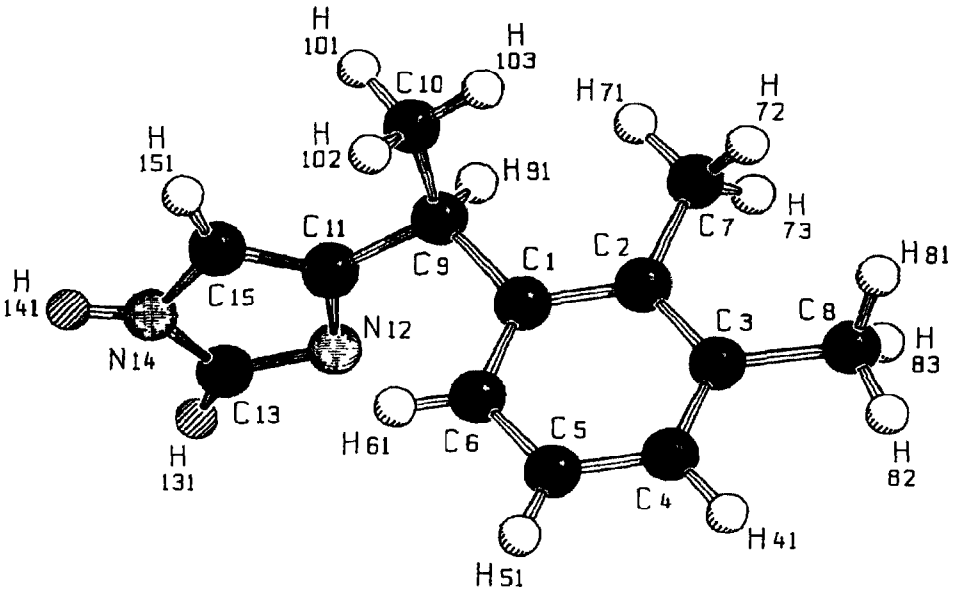


Figure 2. SCHAKAL[26] plot for dexmedetomidine.

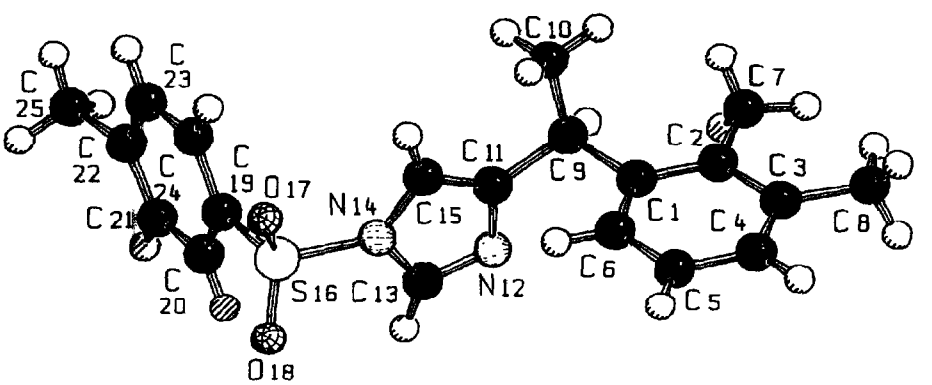


Figure 3. SCHAKAL[26] plot for 1-tosyl-dexmedetomidine.

Table 1: Crystal Data for	(1)	(2)
Molecular formula	$C_{13}H_{16}N_2$	$C_{20}H_{22}N_2O_2S$
Formula weight	200.28	354.47
Crystal Data:		
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a/Å	8.741(2)	8.827(3)
b/Å	9.504(3)	11.562(1)
c/Å	13.894(4)	36.744(3)
α/°	90	90
β/°	90	90
γ/°	90	90
V/Å^3	1154.2(5)	3750(1)
Z	4	8
D_c /g cm^{-3}	1.153	1.256
Linear absorption coeff./cm^{-1}	3.74	6.82
Crystal size/mm	0.15 x 0.15 x 0.20	0.15 x 0.25 x 0.40
Data collection:		
X-radiation	λ = 1.7889 Å, Co-K_α	λ = 1.7889 Å, Co-K_α
θ min., max./°	2, 75	2, 75
ω-scan parameters: A, B (°) (A + B tan θ)	A = 1.20 B = 0.12	A = 0.80 B = 0.12
Scan speed/° min^{-1}	2.0 - 6.7	1.4 - 6.7
Temperature/K	243	295
Collected data	1715	5550
Merged data including Friedel opposities	1391	4801
Observed data, for [I > 3σ (I)]	1224	3944
Merging R	1.02	1.30
Absorption correction, Psi scan	1.16 (min.) 1.30 (max.)	
Diff.abs.	0.791 (min.) 1.534 (max.)	0.796 (min.) 1.495 (max.)
Refinement:		
Solved by	SHELXS-86	SHELXS-86
Weighting scheme: Chebychev	3.02, -3.78, 1.65, -1.49	4.21, -11.10, 2.40, -4.79
Maximum residual electron density/eÅ^{-3}	0.11	0.33
Number of parameters	202	452
Extinction parameter	118(2)	46(2)
Final R	2.80%	4.61%
R_w	1.87%	3.40%

Table 2: Fractional atomic coordinates with standard deviations in parentheses and equivalent isotropic temperature factors U(iso), for dexmedetomidine.

Atom	x	y	z	U(iso)
N(12)	-0.0143(2)	-0.1880(2)	-0.2017(1)	0.0424
N(14)	-0.0489(2)	0.0344(2)	-0.2404(1)	0.0454
C(1)	-0.2649(2)	-0.3405(2)	-0.0810(2)	0.0392
C(2)	-0.2706(2)	-0.4602(2)	-0.0223(2)	0.0425
C(3)	-0.3571(3)	-0.5775(2)	-0.0509(2)	0.0510
C(4)	-0.4379(3)	-0.5720(3)	-0.1353(2)	0.0618
C(5)	-0.4381(3)	-0.4536(4)	-0.1915(2)	0.0635
C(6)	-0.3501(3)	-0.3376(3)	-0.1656(2)	0.0527
C(7)	-0.1888(3)	-0.4658(3)	0.0725(2)	0.0536
C(8)	-0.3608(4)	-0.7098(3)	0.0096(3)	0.0736
C(9)	-0.1734(2)	-0.2103(2)	-0.0520(1)	0.0380
C(10)	-0.2667(3)	-0.1167(3)	0.0158(2)	0.0489
C(11)	-0.1135(2)	-0.1281(2)	-0.1362(2)	0.0375
C(13)	0.0202(3)	-0.0859(2)	-0.2618(2)	0.0453
C(15)	-0.1347(3)	0.0089(2)	-0.1597(2)	0.0436
H(41)	-0.491(3)	-0.663(3)	-0.157(2)	0.078(9)
H(51)	-0.492(3)	-0.449(3)	-0.250(2)	0.079(8)
H(61)	-0.352(3)	-0.253(2)	-0.204(2)	0.053(7)
H(71)	-0.248(4)	-0.496(3)	0.124(2)	0.10(1)
H(72)	-0.132(3)	-0.373(3)	0.093(2)	0.091(9)
H(73)	-0.114(4)	-0.542(4)	0.078(3)	0.13(1)
H(81)	-0.427(4)	-0.781(4)	-0.026(3)	0.13(1)
H(82)	-0.407(4)	-0.692(4)	0.078(3)	0.13(1)
H(83)	-0.252(4)	-0.752(3)	0.018(3)	0.11(1)
H(91)	-0.082(2)	-0.240(2)	-0.017(2)	0.043(6)
H(101)	-0.206(3)	-0.032(3)	0.038(2)	0.072(8)
H(102)	-0.359(3)	-0.078(3)	-0.016(2)	0.067(8)
H(103)	-0.301(3)	-0.170(3)	0.074(2)	0.066(8)
H(131)	0.087(3)	-0.090(3)	-0.314(2)	0.050(7)
H(141)	-0.034(3)	0.124(3)	-0.267(2)	0.057(7)
H(151)	-0.192(3)	0.082(2)	-0.127(1)	0.054(7)

Table 3: Bond lengths (in Å) with standard deviations in parentheses for dexmedetomidine.

N(12) - C(11)	1.380(3)	N(14) - H(141)	0.94(2)
N(12) - C(13)	1.316(3)	C(4) - H(41)	1.02(3)
N(14) - C(13)	1.327(3)	C(5) - H(51)	0.95(3)
N(14) - C(15)	1.371(3)	C(6) - H(61)	0.97(2)
C(1) - C(2)	1.401(3)	C(7) - H(71)	0.93(3)
C(1) - C(6)	1.392(3)	C(7) - H(72)	1.05(3)
C(1) - C(9)	1.527(3)	C(7) - H(73)	0.98(4)
C(2) - C(3)	1.404(3)	C(8) - H(81)	1.02(4)
C(2) - C(7)	1.499(3)	C(8) - H(82)	1.05(4)

C(3) - C(4)	1.371(4)	C(8) - H(83)	1.03(4)
C(3) - C(8)	1.513(4)	C(9) - H(91)	0.98(2)
C(4) - C(5)	1.370(4)	C(10) - H(101)	1.02(3)
C(5) - C(6)	1.391(4)	C(10) - H(102)	0.99(3)
C(9) - C(10)	1.531(3)	C(10) - H(103)	1.00(3)
C(9) - C(11)	1.501(3)	C(13) - H(131)	0.93(2)
C(11) - C(15)	1.355(3)	C(15) - H(151)	0.97(2)

Table 4: Bond angles (in degrees) for the non-hydrogen atoms, with standard deviations in parentheses, for dexmedetomidine.

C(13) - N(12) - C(11)	105.0(2)	C(5)- C(4)- C(3)	121.3(3)
C(15) - N(14) - C(13)	106.3(2)	C(6) - C(5) - C(4)	120.2(3)
C(6) - C(1) - C(2)	119.2(2)	C(5) - C(6) - C(1)	119.9(3)
C(9) - C(1) - C(2)	121.6(2)	C(10) - C(9) - C(1)	110.7(2)
C(9) - C(1) - C(6)	119.2(2)	C(11) - C(9) - C(1)	113.5(2)
C(3) - C(2) - C(1)	119.9(2)	C(11) - C(9) - C(10)	111.3(2)
C(7) - C(2) - C(1)	121.6(2)	C(9) - C(11) - N(12)	121.2(2)
C(7) - C(2) - C(3)	118.5(2)	C(15) - C(11) - N(12)	108.9(2)
C(4) - C(3) - C(2)	119.3(2)	C(15) - C(11) - C(9)	129.8(2)
C(8) - C(3) - C(2)	120.9(3)	N(14) - C(13) - N(12)	112.9(2)
C(8) - C(3) - C(4)	119.7(3)	C(11) - C(15) - N(14)	106.9(2)

Table 5: Selected torsional angles (in degrees) with standard deviations in parentheses for dexmedetomidine.

C(2) - C(1) - C(9) - C(11)	150.53	C(10) - C(9) - C(1) - C(6)	93.58
C(6) - C(1) - C(9) - C(11)	-32.42	C(1) - C(9) - C(11) - N(12)	-60.56
C(7) - C(2) - C(1) - C(6)	-176.28	C(10) - C(9) - C(11) - N(12)	173.73
C(7) - C(2) - C(1) - C(9)	0.78	C(1) - C(9) - C(11) - C(15)	123.47
C(7) - C(2) - C(3) - C(8)	-3.40	C(10) - C(9) - C(11) - C(15)	-2.25
C(8) - C(3) - C(2) - C(1)	177.92	C(9) - C(11) - N(12) - C(13)	-176.88
C(8) - C(3) - C(4) - C(5)	179.51	C(9) - C(11) - C(15) - N(14)	176.66
C(10) - C(9) - C(1) - C(2)	-83.47		

Table 6: Fractional atomic coordinates with standard deviations in parentheses and equivalent isotropic temperature factors U(iso), for the tosyl derivative.

Atom	x	y	z	U(iso)
S(16)	0.3338(1)	0.51819(9)	0.01556(3)	0.0661
S(46)	0.6628(1)	0.36211(9)	0.22607(3)	0.0628
O(17)	0.3332(4)	0.6389(3)	0.00817(8)	0.0792
O(18)	0.4562(4)	0.4446(3)	0.00429(8)	0.0851
O(47)	0.6482(4)	0.4760(3)	0.24053(8)	0.0771
O(48)	0.5455(3)	0.2778(3)	0.23028(8)	0.0782
N(12)	0.0242(6)	0.3404(3)	-0.0299(1)	0.0828
N(14)	0.1816(4)	0.4669(3)	-0.00590(8)	0.0644
N(42)	0.9602(4)	0.1731(3)	0.27270(9)	0.0659
N(44)	0.8138(4)	0.3041(3)	0.24709(8)	0.0568

C(1)	-0.1969(5)	0.4531(3)	-0.0877(1)	0.0580
C(2)	-0.3239(5)	0.4123(3)	-0.1065(1)	0.0629
C(3)	-0.3190(6)	0.4077(4)	-0.1444(1)	0.0691
C(4)	-0.1916(7)	0.4422(4)	-0.1628(1)	0.0753
C(5)	-0.0657(6)	0.4826(4)	-0.1443(1)	0.0793
C(6)	-0.0703(5)	0.4863(4)	-0.1067(1)	0.0707
C(7)	-0.4644(5)	0.3737(5)	-0.0870(1)	0.0834
C(8)	-0.4539(6)	0.3629(5)	-0.1661(1)	0.0955
C(9)	-0.1984(5)	0.4655(3)	-0.0461(1)	0.0607
C(10)	-0.2635(5)	0.5839(4)	-0.0352(1)	0.0708
C(11)	-0.0442(5)	0.4486(3)	-0.0300(1)	0.0616
C(13)	0.1538(7)	0.3533(4)	-0.0153(1)	0.0786
C(15)	0.0489(5)	0.5259(4)	-0.0149(1)	0.0607
C(19)	0.2960(4)	0.4935(3)	0.06149(9)	0.0530
C(20)	0.3402(5)	0.3891(3)	0.0767(1)	0.0599
C(21)	0.3177(5)	0.3718(4)	0.1136(1)	0.0655
C(22)	0.2553(5)	0.4581(4)	0.1351(1)	0.0625
C(23)	0.2096(5)	0.5606(4)	0.1191(1)	0.0653
C(24)	0.2296(4)	0.5781(4)	0.0826(1)	0.0603
C(25)	0.2407(6)	0.4392(5)	0.1755(1)	0.0857
C(31)	1.1784(5)	0.2846(3)	0.3309(1)	0.0544
C(32)	1.3017(5)	0.2481(3)	0.3519(1)	0.0575
C(33)	1.2890(6)	0.2494(4)	0.3901(1)	0.0654
C(34)	1.1564(6)	0.2860(4)	0.4065(1)	0.0721
C(35)	1.0355(6)	0.3224(4)	0.3853(1)	0.0709
C(36)	1.0482(5)	0.3213(3)	0.3482(1)	0.0599
C(37)	1.4466(5)	0.2073(4)	0.3349(1)	0.0756
C(38)	1.4171(6)	0.2056(4)	0.4140(1)	0.0878
C(39)	1.1902(5)	0.2914(3)	0.2893(1)	0.0577
C(40)	1.2623(5)	0.4059(4)	0.2787(1)	0.0698
C(41)	1.0354(5)	0.2790(3)	0.2722(1)	0.0564
C(43)	0.8299(6)	0.1916(3)	0.2577(1)	0.0668
C(45)	0.9473(4)	0.3597(4)	0.2558(1)	0.0558
C(49)	0.7145(4)	0.3714(3)	0.1803(1)	0.0542
C(50)	0.6640(5)	0.2891(4)	0.1559(1)	0.0640
C(51)	0.6986(5)	0.3018(4)	0.1194(1)	0.0704
C(52)	0.7822(5)	0.3948(4)	0.1072(1)	0.0651
C(53)	0.8324(5)	0.4756(4)	0.1321(1)	0.0695
C(54)	0.7992(5)	0.4640(4)	0.1684(1)	0.0654
C(55)	0.8181(7)	0.4114(5)	0.0670(1)	0.0981

Table 7: Bond lengths (in Å) with standard deviations in parentheses for the tosyl derivative.

Molecule 1		Molecule 2	
S(16) - O(17)	1.422(3)	S(46) - O(47)	1.426(3)
S(16) - O(18)	1.437(3)	S(46) - O(48)	1.430(3)
S(16) - N(14)	1.666(4)	S(46) - N(44)	1 681(3)
S(16) - C(19)	1.744(4)	S(46) - C(49)	1.747(4)
N(12) - C(11)	1.389(6)	N(42) - C(41)	1.393(5)
N(12) - C(13)	1.272(6)	N(42) - C(43)	1.293(5)
N(14) - C(13)	1.380(5)	N(44) - C(43)	1.365(5)
N(14) - C(15)	1.395(5)	N(44) - C(45)	1.380(5)
C(1) - C(2)	1.397(6)	C(31) - C(32)	1.399(5)
C(1) - C(6)	1.373(5)	C(31) - C(36)	1.379(5)
C(1) - C(9)	1.538(5)	C(31) - C(39)	1.536(5)
C(2) - C(3)	1.397(5)	C(32) - C(33)	1.409(6)
C(2) - C(7)	1.500(6)	C(32) - C(37)	1.499(6)
C(3) - C(4)	1.371(7)	C(33) - C(34)	1.382(7)
C(3) - C(8)	1.522(6)	C(33) - C(38)	1.516(6)
C(4) - C(5)	1.383(7)	C(34) - C(35)	1.386(6)
C(5) - C(6)	1.383(6)	C(35) - C(36)	1.370(5)
C(9) - C(10)	1.537(6)	C(39) - C(40)	1.520(5)
C(9) - C(11)	1.496(6)	C(39) - C(41)	1.512(5)
C(11) - C(15)	1.334(5)	C(41) - C(45)	1.355(5)
C(19) - C(20)	1.386(5)	C(49) - C(50)	1.380(5)
C(19) - C(24)	1.378(5)	C(49) - C(54)	1.377(5)
C(20) - C(21)	1.384(5)	C(50) - C(51)	1.383(5)
C(21) - C(22)	1.388(6)	C(51) - C(52)	1.379(6)
C(22) - C(23)	1.385(5)	C(52) - C(53)	1.378(6)
C(22) - C(25)	1.506(5)	C(52) - C(55)	1.523(6)
C(23) - C(24)	1.368(5)	C(53) - C(54)	1.373(6)

Table 8: Bond angles (in degrees) for the non-hydrogen atoms, with standard deviations in parentheses, for the tosyl derivative.

Molecule 1		Molecule 2	
O(18) - S(16) - O(17)	121.9(2)	O(48) - S(46) - O(47)	121.6(2)
N(14) - S(16) - O(17)	104.8(2)	N(44) - S(46) - O(47)	105.6(2)
N(14) - S(16) - O(18)	105.0(2)	N(44) - S(46) - O(48)	104.6(2)
N(14) - S(16) - C(19)	104.2(2)	N(44) - S(46) - C(49)	105.1(2)
C(19) - S(16) - O(17)	110.2(2)	C(49) - S(46) - O(47)	109.0(2)
C(19) - S(16) - O(18)	109.0(2)	C(49) - S(46) - O(48)	109.6(2)
C(13) - N(12) - C(11)	106.7(4)	C(43) - N(42) - C(41)	105.8(3)
C(13) - N(14) - S(16)	126.9(4)	C(43) - N(44) - S(46)	126.4(3)
C(15) - N(14) - S(16)	128.0(3)	C(45) - N(44) - S(46)	126.7(3)
C(15) - N(14) - C(13)	104.8(4)	C(45) - N(44) - C(43)	106.8(3)
C(6) - C(1) - C(2)	119.8(4)	C(36) - C(31) - C(32)	119.2(4)
C(9) - C(1) - C(2)	121.0(4)	C(39) - C(31) - C(32)	120.8(4)

C(9) - C(1) - C(6)	119.1(4)	C(39) - C(31) - C(36)	119.9(3)
C(3) - C(2) - C(1)	118.7(4)	C(33) - C(32) - C(31)	119.0(4)
C(7) - C(2) - C(1)	122.0(4)	C(37) - C(32) - C(31)	121.9(4)
C(7) - C(2) - C(3)	119.3(4)	C(37) - C(32) - C(33)	119.1(4)
C(4) - C(3) - C(2)	120.4(4)	C(34) - C(33) - C(32)	120.3(4)
C(8) - C(3) - C(2)	120.6(5)	C(38) - C(33) - C(32)	120.8(4)
C(8) - C(3) - C(4)	119.0(4)	C(38) - C(33) - C(34)	118.9(4)
C(5) - C(4) - C(3)	121.1(4)	C(35) - C(34) - C(33)	120.1(4)
C(6) - C(5) - C(4)	118.5(5)	C(36) - C(35) - C(34)	119.6(4)
C(5) - C(6) - C(1)	121.5(5)	C(35) - C(36) - C(31)	121.9(4)
C(10) - C(9) - C(1)	110.2(3)	C(40) - C(39) - C(31)	109.2(3)
C(11) - C(9) - C(1)	111.9(3)	C(41) - C(39) - C(31)	110.4(3)
C(11) - C(9) - C(10)	110.7(3)	C(41) - C(39) - C(40)	110.7(3)
N(12) - C(11) - C(9)	121.0(4)	N(42) - C(41) - C(39)	120.6(3)
N(12) - C(11) - C(15)	109.5(4)	N(42) - C(41) - C(45)	109.8(4)
C(15) - C(11) - C(9)	129.5(4)	C(45) - C(41) - C(39)	129.6(4)
N(14) - C(13) - N(12)	112.1(4)	N(44) - C(43) - N(42)	111.8(4)
N(14) - C(15) - C(11)	106.8(4)	N(44) - C(45) - C(41)	105.8(4)
C(20) - C(19) - S(16)	118.6(3)	C(50) - C(49) - S(46)	119.8(3)
C(24) - C(19) - S(16)	120.6(3)	C(54) - C(49) - S(46)	119.7(3)
C(24) - C(19) - C(20)	120.8(4)	C(54) - C(49) - C(50)	120.4(4)
C(21) - C(20) - C(19)	118.6(4)	C(51) - C(50) - C(49)	118.9(4)
C(22) - C(21) - C(20)	120.8(4)	C(52) - C(51) - C(50)	121.1(4)
C(23) - C(22) - C(21)	119.1(4)	C(53) - C(52) - C(51)	119.0(4)
C(25) - C(22) - C(21)	119.6(4)	C(55) - C(52) - C(51)	121.7(4)
C(25) - C(22) - C(23)	121.3(4)	C(55) - C(52) - C(53)	119.3(5)
C(24) - C(23) - C(22)	120.5(4)	C(54) - C(53) - C(52)	120.6(4)
C(23) - C(24) - C(19)	120.0(4)	C(53) - C(54) - C(49)	120.0(4)

Table 9: Selected torsional angles (in degrees) with standard deviations in parentheses, for the tosyl derivative.

Molecule 1		Molecule 2	
O(17) - S(16) - C(19) - C(20)	-158.67	O(47) - S(46) - C(49) - C(50)	-146.95
O(17) - S(16) - C(19) - C(24)	18.51	O(47) - S(46) - C(49) - C(54)	29.88
O(18) - S(16) - C(19) - C(20)	-22.39	O(48) - S(46) - C(49) - C(50)	-11.64
O(18) - S(16) - C(19) - C(24)	154.79	O(48) - S(46) - C(49) - C(54)	165.18
N(14) - S(16) - C(19) - C(20)	89.35	N(44) - S(46) - C(49) - C(50)	100.27
N(14) - S(16) - C(19) - C(24)	-93.47	N(44) - S(46) - C(49) - C(54)	-82.90
C(13) - N(14) - S(16) - O(17)	161.25	C(43) - N(44) - S(46) - O(47)	143.58
C(13) - N(14) - S(16) - O(18)	31.62	C(43) - N(44) - S(46) - O(48)	14.16
C(13) - N(14) - S(16) - C(19)	-82.97	C(43) - N(44) - S(46) - C(49)	-101.25
C(15) - N(14) - S(16) - O(17)	-25.87	C(45) - N(44) - S(46) - O(47)	-38.87
C(15) - N(14) - S(16) - O(18)	-155.50	C(45) - N(44) - S(46) - O(48)	-168.29
C(15) - N(14) - S(16) - C(19)	89.90	C(45) - N(44) - S(46) - C(49)	76.30
C(2) - C(1) - C(9) - C(11)	149.89	C(32) - C(31) - C(39) - C(41)	154.35
C(6) - C(1) - C(9) - C(11)	-32.33	C(36) - C(31) - C(39) - C(41)	-29.51

C(7) - C(2) - C(1) - C(6)	179.32	C(37) - C(32) - C(31) - C(36)	-179.95
C(7) - C(2) - C(1) - C(9)	-2.91	C(37) - C(32) - C(31) - C(39)	-3.79
C(7) - C(2) - C(3) - C(8)	-0.65	C(37) - C(32) - C(33) - C(38)	-2.52
C(8) - C(3) - C(2) - C(1)	179.39	C(38) - C(33) - C(32) - C(31)	177.27
C(8) - C(3) - C(4) - C(5)	-179.42	C(38) - C(33) - C(34) - C(35)	-177.62
C(10) - C(9) - C(1) - C(2)	-86.49	C(40) - C(39) - C(31) - C(32)	-83.67
C(10) - C(9) - C(1) - C(6)	91.30	C(40) - C(39) - C(31) - C(36)	92.47
C(1) - C(9) - C(11) - N(12)	-69.66	C(31) - C(39) - C(41) - N(42)	-70.56
C(10) - C(9) - C(11) - N(12)	166.96	C(40) - C(39) - C(41) - N(42)	168.37
C(1) - C(9) - C(11) - C(15)	108.95	C(31) - C(39) - C(41) - C(45)	107.37
C(10) - C(9) - C(11) - C(15)	-14.43	C(40) - C(39) - C(41) - C(45)	-13.70
C(9) - C(11) - N(12) - C(13)	178.71	C(39) - C(41) - N(42) - C(43)	177.14
C(9) - C(11) - C(15) - N(14)	-177.06	C(39) - C(41) - C(45) - N(44)	-176.30
N(12) - C(13) - N(14) - S(16)	176.70	N(42) - C(43) - N(44) - S(46)	179.04
C(11) - C(15) - N(14) - S(16)	-176.56	C(41) - C(45) - N(44) - S(46)	-179.68
S(16) - C(19) - C(20) - C(21)	176.60	S(46) - C(49) - C(50) - C(51)	176.15
S(16) - C(19) - C(24) - C(23)	-175.70	S(46) - C(49) - C(54) - C(53)	-175.99
C(20) - C(21) - C(22) - C(25)	-176.39	C(50) - C(51) - C(52) - C(55)	-178.57
C(24) - C(23) - C(22) - C(25)	177.23	C(54) - C(53) - C(52) - C(55)	178.76

Experimental

General Methods. Melting points were recorded on a Büchi 510 Melting Point apparatus. One-dimensional proton nuclear magnetic resonance (δ_H) spectra, ^{13}C nuclear magnetic resonance (δ_C) spectra, and two-dimensional H,C-correlated NMR spectra were recorded on a Bruker AC 300 P spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). The multiplicities were assigned using DEPT sequence. NMR spectra were run in deuterochloroform referenced to TMS as an internal standard. All chemical shifts are quoted on the δ-scale. Infrared spectra were recorded on a Mattson Galaxy 2020 FT–IR spectrophotometer. Mass spectra and HRMS were recorded on a Kratos MS 80 RF Autoconsole spectrometer using electron impact ionization (75 eV, EI). Optical rotations were measured on a Jasco DIP-360 digital polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. The HPLC system 1 consisted of a fully automated HP 1090 Series M liquid chromatograph, a DR5 binary pump, and a variable volume autoinjector + autosampler (Hewlett–Packard, USA). The column used for chiral separations was a Chiral AGP 4 x 100 mm stainless steel column (packed with 5-μm spherical silica particles, Cromtech AB, Sweden). The mobile phase was 30 mM ammonium hydrogen phosphate/potassium dihydrogen phosphate buffer (pH 7.5)–HPLC-grade acetonitrile–methanol (200:40:10 v/v) or 30 mM potassium dihydrogen phosphate/disodium hydrogen phosphate buffer (pH 7.0)–HPLC-grade acetonitrile (800:200 v/v). The flow rate was set at 0.5 and 0.8 ml/min respectively. The column used for chromatographic purity analyses was Nova-Pak Phenyl, Radial-Pak 8 x 100 mm cartridge (Waters, USA). The mobile phase for chromatographic purity analyses was 40 mM ammonium hydrogen phosphate buffer (pH 7.5)–HPLC-grade acetonitrile–methanol–tetrahydrofuran (300:50:75:90 v/v or 180:30:45:152 v/v). The flow rate was 1.3 ml/min. The HPLC system 2 consisted of an LKB HPLC pump (LKB, Sweden), a Beckman System Gold programmable detector module 166 with NEC PC-8300 data processor, and a Merck Hitachi D–2000 Chromato-integrator. The column used for chiral separations of 1-tosyl derivatives was Bakerbond Chiral Phase DNBPG (Covalent) Chiral 4.6 x 250 mm steel column (packed with 5-μm spherical aminopropyl silica particles; pore size 110 Å, J.T. Baker, USA). The mobile phase was HPLC-

grade hexane–isopropanol (180:20 v/v). The flow rate was 1.4 ml/min. All separations were carried out at ambient temperature. Thin layer chromatography was carried out on glass plates coated with $60F_{254}$ silica (0.25 mm). The eluent was dichloromethane–methanol–ammonia (90:10:0.5) and plates were developed using Payly's reagent. Solvents and commercially available reagents for synthesis were reagent grade and solvents for chromatography were purchased from FSA Laboratory Supplies (England). The HVLP 0.45-μm filters used for mobile phase filtration were obtained from Millipore (Molsheim, France). The water was deionized, ultrafiltered, reverse osmosis water, prepared in-house. Dexmedetomidine (99.6% ee), levomedetomidine (99.6% ee), and racemic medetomidine were manufactured by Orion Corporation FARMOS (Oulu, Finland).

(+)-(S)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole. Toluene-4-sulfonyl chloride (1.9 g, 10 mmol) was dissolved in triethylamine–dichloromethane (1.0 g, 10 mmol/20 ml) solution. This mixture was added dropwise to a dexmedetomidine base–dichloromethane solution (2.0 g, 10 mmol/10 ml) at room temperature. The reaction mixture was stirred at that temperature for 2.5 hours and the reaction was followed by thin layer chromatography. Water was added and the organic phase was separated. The organic phase was washed with water and evaporated to dryness. The residual was dissolved in warm ethyl acetate (20 ml) and crystallized without stirring. The crystallized product was filtered and washed with ethyl acetate. Recrystallization from ethyl acetate gave (+)-(S)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole, 1.1 g, 31.1%, as white crystalline solid, m.p. 129-131 °C; optical purity ~100% ee (HPLC), $[\alpha]_D^{20}$ +98.8 (c, 1.0 in MeOH); chromatographic purity 98.49% (HPLC); υ_{max}(KBr) 1174.7 cm^{-1} (s, $-SO_2-N$); δ_H($CDCl_3$): 1.52 (3H, d, J 7 Hz, C10–Me), 2.17 (3H, s, C8–Me), 2.27 (3H, s, C7–Me), 2.43 (3H, s, C25–Me), 4.31 (1H, q, J 7 Hz, H–91), 6.86 (1H, s, H–151), 6.93–6.97 (1H, m, H–61), 7.00–7.25 (2H, m, H–41, H–51), 7.33 (2H, d, J 8 Hz, H–211, H–231, AB), 7.78 (2H, d, J 8 Hz, H–201, H–241, AB), 7.93 (1H, d, J 1 Hz, H–131); δ_C ($CDCl_3$): 14.87 (q, C–8), 20.37 (q, C–10), 20.99 (q, C–7), 21.70 (q, C–25), 35.21 (d, C–9), 113.11 (d, C–15), 124.41 (d, C–6), 125.56 (d, C–5), 127.26 (dd, C–20,C–24), 128.17 (d, C–4), 130.34 (dd, C–21, C–23), 134.13, 135.11, 136.88 (3 x s, C–22, C–19, C–2), 136.43 (d, C–13), 142.06 (s, C–3), 146.04 (s, C–11), 150.04 (s, C–1); m/z (75 eV, EI) 354 (M, 17%), 199 (M-tosyl, 100%), HRMS measured 354.1369, calculated for $C_{20}H_{22}N_2O_2S$ 354.14019.

(–)-(R)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole was synthesized by the method described above, using levomedetomidine as starting material. The yield was 1.1 g, 31.1%, white crystalline solid, m.p. 128-130 °C; optical purity ~100% ee (HPLC), $[\alpha]_D^{20}$ –98.8 (c, 1.0 in MeOH); chromatographic purity 98.44% (HPLC). The IR, NMR, and MS spectra were identical with those of the (+)-(S) isomer. This isomer was used as a reference in HPLC analysis.

(±)-(R,S)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole was synthesized by the method described above, using racemic medetomidine as starting material. The yield was 1.1 g, 31.1%, white crystalline solid, m.p. 125-126 °C, optical purity ~0% ee (HPLC), $[\alpha]_D^{20}$ ±0.0 (c, 1.0 in MeOH); chromatographic purity 98.27% (HPLC). The IR, NMR, and MS spectra were identical with those of the (+)-(S) and (–)-(R) isomer. This isomer was used as a reference in HPLC analysis.

Detosylation procedure for 1-tosyl derivatives of (d)-, (l)- and (d,l)-medetomidine

A mixture of (+)-(S)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole (0.6 g, 1.7 mmol), methanol (20 ml) and sodium hydroxide (0.19 g, 3.4 mmol) was stirred for 1 hour at 40 °C. The reaction was followed by TLC. Water (30 ml) was added and methanol was evaporated. The precipitated product was filtered, washed with water (3 x 20 ml), and dried to constant weight at 50 °C in a vacuum oven. The detosylation gave dexmedetomidine base as white crystalline solid 0.3 g (88.5%), m.p. 145-147 °C, optical purity ~100% ee (HPLC), $[\alpha]_D^{20}$ +75.2; chromatographic purity 99.96% (HPLC). The IR, NMR, and MS spectra were

identical with those of the dexmedetomidine base used for this investigation.

Detosylation of (–)-(R)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole gave levomedetomidine as white crystalline solid 0.3 g (88.5%), m.p. 146-148 °C (149–151 °C), optical purity 100% ee (HPLC), $[\alpha]_D^{20}$ -75.2; chromatographic purity 99.97% (HPLC). The IR, NMR, and MS spectra were identical with those of the levomedetomidine base used for this investigation.

Detosylation of (±)-(R,S)-4-[1-(2,3-dimethylphenyl)ethyl]-1-tosyl-1*H*-imidazole gave medetomidine base as white crystalline solid 0.3 g (88.5%), optical purity ~0% ee (HPLC), $[\alpha]_D^{20}$ ±0; chromatographic purity 96.78% (HPLC). The IR, NMR, and MS spectra were identical with those of medetomidine.

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