

# Synthesis and Resolution of *cis*-2-(1-Hydroxy-1-methylethyl)-5-methylpyrrolidine and X-Ray Crystal Structure of its (*S*)-Mandelate Salt

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A useful stereoselective method for the preparation and resolution of the unsymmetrically substituted pyrrolidine-based aminol **3**, *cis*-2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidine, is described. The molecular conformation and absolute configuration of resolved (–)-**3** were determined by single-crystal X-ray diffraction analysis of its (*S*)-(+)-mandelate salt. The crystals have orthorhombic symmetry (*P*<sub>2</sub><sub>1</sub><sub>2</sub><sub>1</sub>). The unit cell with dimensions *a* = 9.622(1), *b* = 16.707(1), *c* = 20.529(2) Å, contains eight formula units. The two chiral centres in the pyrrolidine ring, carrying the 1-hydroxy-1-methylethyl and the methyl substituents, respectively, both have the *S* configuration. The two crystallographically independent ion pairs differ only in the conformation of the mandelate phenyl moiety. The crystal structure consists of hydrogen-bonded layers held together by weak Van der Waal's type forces. The structural model has been refined to a linear *R* value of 0.051 for 2425 reflections.

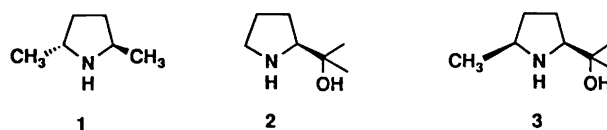
Pyrrolidine-based chiral auxiliaries have attracted much attention over the last decade.<sup>1</sup> Their preparation relies on resolution procedures, or synthetic transformations often employing optically active amino acid precursors. Thus an efficient six-step synthesis of either antipode of *trans*-2,5-dimethylpyrrolidine (**1**) from D- and L-alanine, respectively, has been reported.<sup>2</sup>

Because of our interest in the use of the aminol **2** as a chiral auxiliary in asymmetric alkylations<sup>3</sup> and aldol condensations,<sup>4</sup> we needed new, structurally related, aminols to explain and improve earlier results. One of these analogues was the 5-methyl substituted aminol **3**.

We have now developed a practical stereoselective synthesis of *cis*-2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidine (**3**) from simple starting materials. The method followed here allows the preparation and resolution of **3** on a multi-gram scale without using chromatographic separations.

The title compound, in *N*-benzylated form (**8**), was obtained via a four-step stereoselective sequence starting from diester **4** (a *cis/trans* mixture), which was readily prepared in two steps from adipic acid.<sup>5,6</sup> The synthesis was carried out without isolation of the intermediates **5–7**, thus avoiding tedious separation procedures.

The symmetrical diester **4** (*cis/trans* = 1/2) was converted into the bifunctionalized pyrrolidine **5** by addition of methyl magnesium iodide (3 equiv.) (Scheme 1). The crude product **5** was then treated with an excess of LiAlH<sub>4</sub> to



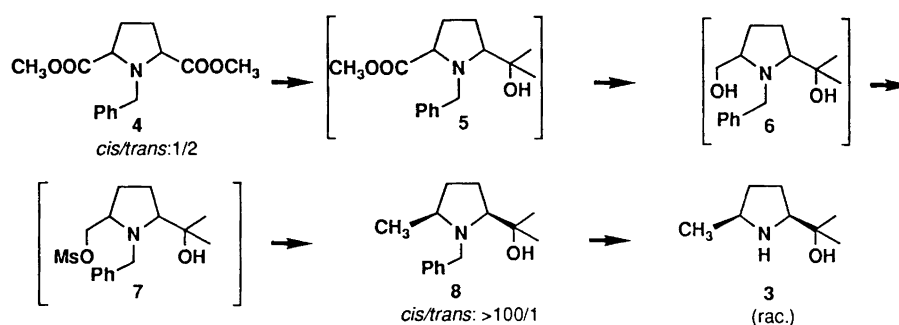
afford the diol **6** as a viscous oil. This oil was transformed into the crude *cis*-aminol **8** via the methanesulfonate **7**. Finally, distillation or chromatography gave pure *cis*-**8** (*cis/trans* > 100/1) in 30% overall yield based on *cis*-**4**.

A preliminary gas chromatographic analysis of the products **4**, **5**, **6** and **8** indicated that enrichment of the *cis* isomers takes place mainly in the reduction steps and the aqueous work-up of reaction products.

Hydrogenation of **8** furnished racemic *cis*-aminol **3** in 71% isolated yield after distillation. Resolution of **3** was achieved via its mandelate salt in acetone. The (*S*)-(+)-mandelate salt yields (–)-**3**. The absolute configuration of (–)-**3** was determined by a single-crystal X-ray diffraction analysis of its (*S*)-(+)-mandelate salt.

Two crystallographically independent ion pairs, A and B (cf. Fig. 1), were identified in the crystals. All observed values of bond lengths and bond angles in the two conformers (Tables 2 and 3) are comparable to each other to within experimental error and generally also conform to the values previously published for the related *trans*-(2*R*, 5*R*)-2,5-dimethylpyrrolidinium (*S*)-mandelate structure.<sup>7</sup> The aromatic rings are planar to within 0.010 and 0.012 Å in the A and B forms, respectively. The conformation of the pyrroli-

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Scheme 1.

dine ring is intermediate between envelope ( $C_s$  symmetry) and half-chair conformation ( $C_2$  symmetry) in both forms. The ring puckering parameters, calculated according to

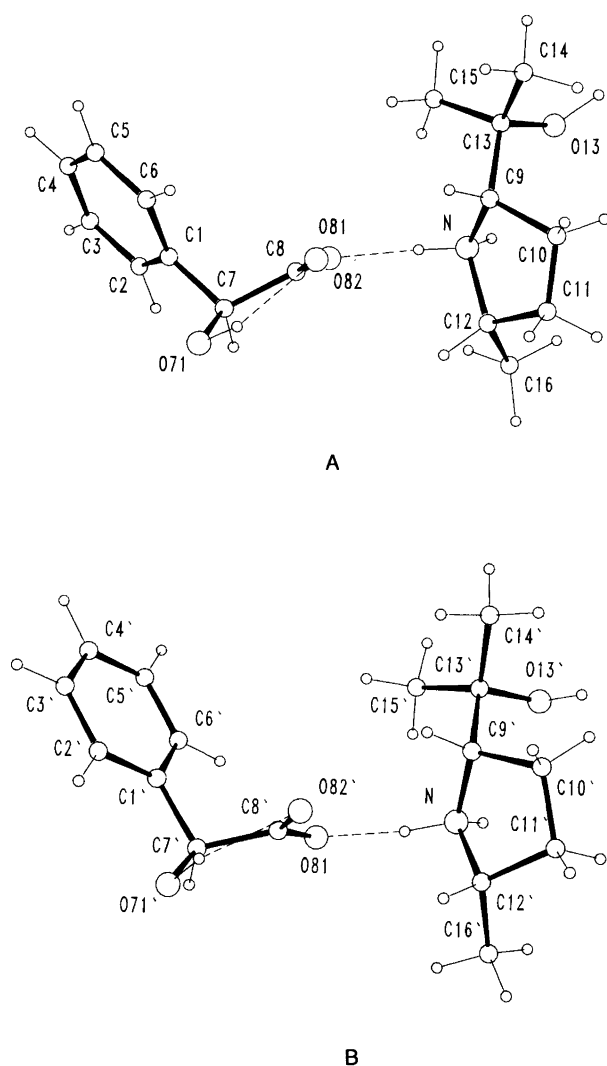


Fig. 1. Perspective views of the two crystallographically independent ion pairs in the crystal structure of  $(-)$ -(2*S*,5*S*)-2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidinium (*S*)-mandelate, with atoms numbered as in the text.

Cremer and Pople<sup>8</sup> for the A and the B units, are  $Q = 0.301(5)$  and  $0.394(6)$  Å and  $\Phi = -154(2)$  and  $154(1)^\circ$ , respectively. An intramolecular hydrogen bond locks the carboxy and the hydroxy groups of the mandelate moiety in a rigid conformation by formation of a five-membered ring (including the H atom). Another strong, approximately linear, hydrogen bond binds the mandelate anion to the pyrrolidinium cation, just as in the structure of the *trans*-2,5-dimethylpyrrolidinium mandelate.<sup>7</sup> The carboxy group is nearly perpendicular to the pyrrolidine ring plane. The calculated dihedral angles, formed by the least-squares (LS) planes through the five pyrrolidine ring atoms and the  $-\text{COO}$  moiety, are  $97.4(5)^\circ$  [in the A form] and  $95.8(4)^\circ$  [in the B form]. The only significant difference between the two symmetrically independent formula units is the conformation of the phenyl moiety. The dihedral angles formed by the LS-planes through the phenyl ring and the  $-\text{COO}$  group are  $75.5(6)$  and  $103.9(4)^\circ$  in the A and the B conformers, respectively. The torsional angles calculated for the C(2)–C(1)–C(7)–C(8) and the C(6)–C(1)–C(7)–C(8) bonds (right-hand rule according to Klyne and Prelog,<sup>9</sup> e.s.d.'s following Stanford and Waser<sup>10</sup>), are  $118.6(5)$  and  $63.1(6)^\circ$  in the A and  $-120.6(5)$  and  $58.4(6)^\circ$  in the B form. Accordingly, the present B conformer can be derived from the A form by rotation of the phenyl group approximately  $120^\circ$  around the C(1)–C(7) bond.

In the crystal structure, both the A and the B ion pairs form infinite hydrogen-bonded chains in the crystallographic *c* direction. These chains are then cross-linked via hydrogen bonds between A and B units so as to form infinite layers, shown in Fig. 2. In the hydrogen-bonding scheme obtained, the mandelate hydroxy H atoms, H(71) and H(71'), participate in bifurcated hydrogen bonds. The carboxylate O(82) atom in both conformers functions as an acceptor for two hydrogen bonds (cf. Table 4). The hydrogen bonds give rise to two fairly short non-bonded contacts,  $\text{O}(82)\cdots\text{O}(13')_{x+1,y,z} = 3.226(5)$  and  $\text{O}(82')\cdots\text{O}(13)_{x-1,y,z} = 3.238(4)$  Å and there are also some other distances within the layer in the range of 3.4–3.5 Å between the non-hydrogen atoms. The interatomic distances between the layers are, however, longer ( $> 3.6$  Å), which indicates weaker intermolecular forces between the layers.

**Table 1.** Fractional atomic coordinates and equivalent<sup>a</sup>/isotropic temperature factors of the non-hydrogen atoms and of the hydrogens involved in hydrogen bonds in the crystal structure of (–)-*cis*-2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidinium (S)-mandelate. The e.s.d.'s, where given,<sup>b</sup> are in parentheses.

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	( <i>U</i> <sub>eq</sub> <sup>a</sup> / <i>U</i> ) /Å <sup>2</sup>
C(1)	–0.3022(5)	–0.1521(3)	–0.1672(2)	0.045(2)
C(2)	–0.4180(6)	–0.1792(4)	–0.1996(3)	0.057(2)
C(3)	–0.4333(7)	–0.2609(4)	–0.2141(3)	0.078(3)
C(4)	–0.3317(9)	–0.3139(4)	–0.1961(3)	0.082(3)
C(5)	–0.2148(8)	–0.2880(4)	–0.1636(4)	0.083(3)
C(6)	–0.2006(6)	–0.2064(4)	–0.1499(3)	0.070(3)
C(7)	–0.2842(5)	–0.0635(3)	–0.1523(2)	0.048(2)
O(7)	–0.1639(4)	–0.0351(2)	–0.1848(3)	0.066(2)
C(8)	–0.2765(6)	–0.0476(3)	–0.0790(2)	0.051(2)
O(8)	–0.3870(4)	–0.0492(3)	–0.0484(2)	0.085(2)
O(82)	–0.1608(4)	–0.0316(3)	–0.0556(2)	0.063(2)
N	–0.3755(4)	0.0370(3)	0.0604(2)	0.049(2)
C(9)	–0.2530(5)	0.0192(3)	0.1020(3)	0.049(2)
C(10)	–0.2124(7)	0.1008(4)	0.1300(4)	0.088(3)
C(11)	–0.2574(9)	0.1576(5)	0.0823(6)	0.200(7)
C(12)	–0.3549(7)	0.1216(4)	0.0338(3)	0.071(3)
C(13)	–0.2850(6)	–0.0457(4)	0.1518(3)	0.058(2)
O(13)	–0.3973(4)	–0.0187(3)	0.1934(2)	0.073(2)
C(14)	–0.1562(7)	–0.0610(5)	0.1924(3)	0.092(3)
C(15)	–0.3385(8)	–0.1209(4)	0.1172(4)	0.095(3)
C(16)	–0.4902(7)	0.1651(4)	0.0276(4)	0.092(3)
C(1')	–0.7290(6)	0.1462(3)	0.1851(3)	0.054(2)
C(2')	–0.6113(7)	0.1761(4)	0.2163(3)	0.074(3)
C(3')	–0.5793(9)	0.2565(5)	0.2108(4)	0.100(4)
C(4')	–0.6636(10)	0.3075(5)	0.1763(4)	0.105(4)
C(5')	–0.7799(9)	0.2786(4)	0.1458(4)	0.090(3)
C(6')	–0.8146(7)	0.1980(4)	0.1500(3)	0.072(3)
C(7')	–0.7642(5)	0.0571(3)	0.1879(2)	0.047(2)
C(71')	–0.6675(4)	0.0123(2)	0.2258(2)	0.057(2)
C(8')	–0.7685(5)	0.0238(3)	0.1184(2)	0.043(2)
O(81')	–0.8853(4)	0.0234(3)	0.0909(2)	0.061(2)
O(82')	–0.6579(4)	–0.0011(2)	0.0946(2)	0.057(2)
N'	–0.8740(4)	–0.0546(3)	–0.0217(2)	0.046(2)
C(9')	–0.7578(5)	–0.0232(3)	–0.0635(3)	0.052(2)
C(10')	–0.7056(7)	–0.0957(4)	–0.1027(3)	0.086(3)
C(11')	–0.7777(8)	–0.1664(4)	–0.0747(4)	0.105(4)
C(12')	–0.8353(7)	–0.1401(3)	–0.0077(3)	0.076(3)
C(13')	–0.8058(6)	0.0489(4)	–0.1041(3)	0.064(2)
O(13')	–0.9094(4)	0.0238(3)	–0.1493(2)	0.070(2)
C(14')	–0.6796(7)	0.0819(5)	–0.1415(3)	0.106(4)
C(15')	–0.8750(7)	0.1117(4)	–0.0614(3)	0.079(3)
C(16')	–0.9581(8)	–0.1874(4)	0.0174(4)	0.091(3)
H(71)	–0.1136	–0.0193	–0.1468	0.08(2)
H(N1)	–0.3874	0.0042	0.0231	0.10(2)
H(N2)	–0.4554	0.0376	0.0846	0.06(2)
H(13)	–0.3870	–0.0152	0.2428	0.20(4)
H(71')	–0.6017	0.0002	0.1914	0.10(3)
H(N1')	–0.8835	–0.0286	0.0214	0.06(2)
H(N2')	–0.9547	–0.0530	–0.0449	0.04(2)
H(13')	–0.8753	–0.0060	–0.1817	0.09(3)

<sup>a</sup> $U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$ . <sup>b</sup>The H atom positions are not refined (cf. the text).

**Table 2.** Intramolecular bond distances between the non-hydrogen atoms in the crystal structure of (–)-*cis*-2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidinium (S)-mandelate. The e.s.d.s are given in parentheses.

Atoms	Distance/Å	
	A	B
C(1)–C(2)	1.375(7)	1.394(9)
C(1)–C(6)	1.380(8)	1.395(8)
C(1)–C(7)	1.521(7)	1.527(7)
C(2)–C(3)	1.404(8)	1.384(10)
C(3)–C(4)	1.369(10)	1.373(12)
C(4)–C(5)	1.378(10)	1.370(12)
C(5)–C(6)	1.399(9)	1.390(9)
C(7)–C(71)	1.418(6)	1.426(6)
C(7)–C(8)	1.529(6)	1.532(6)
C(8)–C(81)	1.235(6)	1.258(6)
C(8)–O(82)	1.242(6)	1.242(6)
N–C(9)	1.486(6)	1.505(6)
N–C(12)	1.527(7)	1.503(7)
C(9)–C(10)	1.529(8)	1.538(8)
C(9)–C(13)	1.522(7)	1.536(8)
C(10)–C(11)	1.430(12)	1.486(10)
C(11)–C(12)	1.494(12)	1.547(10)
C(12)–C(16)	1.496(9)	1.513(10)
C(13)–O(13)	1.449(6)	1.425(7)
C(13)–C(14)	1.515(8)	1.539(9)
C(13)–C(15)	1.532(8)	1.521(8)

## Experimental

<sup>1</sup>H NMR spectra were recorded for CDCl<sub>3</sub> solutions on a Bruker WP200 (200 MHz) spectrometer with tetramethylsilane (Me<sub>4</sub>Si) as an internal standard. GLC analyses were performed on a Pye Unicam Series 204 instrument using a DB 5 coated fused silica capillary column. A Perkin-Elmer 241 polarimeter was used for optical rotation measurements. Boiling and melting points are uncorrected. Unless otherwise stated, chemicals were used as obtained from commercial sources without further purification.

*cis*-N-Benzyl-2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidine (**8**). Freshly distilled diester **4**<sup>5,6</sup> (19.6 g, GLC purity 92.6%, 65.8 mmol, *trans/cis* = 67/33 according to GLC) and diethyl ether (200 ml) were introduced under nitrogen into a 2 l, three-necked, round-bottomed flask, equipped with condenser, addition funnel and efficient stirring. CH<sub>3</sub>MgI (3 equiv.), prepared from CH<sub>3</sub>I (33.1 g, 233 mmol) and Mg (5.15 g, 212 mmol) in diethyl ether (200 ml), was added dropwise (15 min) to the rapidly stirred solution of **4** at 0°C, followed by additional diethyl ether (500 ml). The resulting thick slurry was refluxed (3 h), stirred overnight at room temp., cooled in an ice-bath and quenched by addition of aqueous NH<sub>4</sub>Cl (sat., 300 ml) followed by additional water (100 ml) to dissolve all solid material. The phases were separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×200 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford crude **5** (17.7 g, GLC purity 63.5%, *cis/trans* =

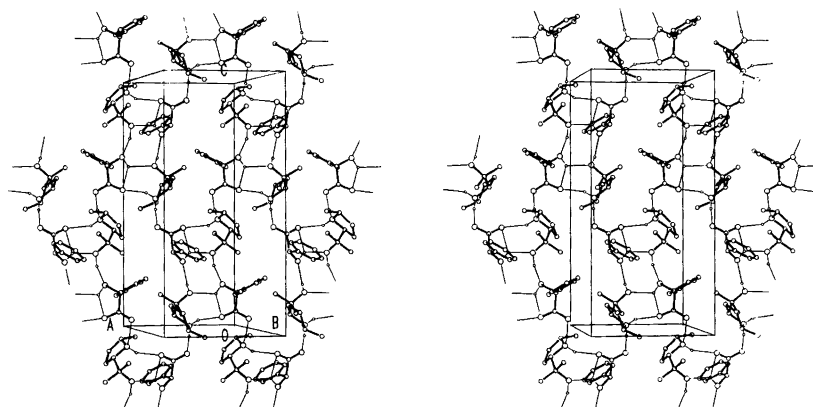


Fig. 2. Stereoscopic illustration of a characteristic layer fragment in the crystal structure of  $(-)-(2S,5S)$ -2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidinium (*S*)-mandelate. The hydrogens, except those involved in hydrogen bonds, are omitted for clarity.

66/34) as a light brown oil. This oil was dissolved<sup>11</sup> in diethyl ether (250 ml) and added dropwise (10 min) to a slurry of  $\text{LiAlH}_4$  (10.2 g, 269 mmol) in diethyl ether (150 ml) kept under  $\text{N}_2$  at room temp. The reaction was stirred for 2 h, cooled in an ice-bath and quenched<sup>12</sup> by cautious

Table 3. Intramolecular bond angles involving the non-hydrogen atoms in the crystal structure of  $(-)-cis$ -2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidinium (*S*)-mandelate. The e.s.d.'s are given in parentheses.

Atoms	Angle/°	
	A	B
C(6)–C(1)–C(7)	120.4(5)	119.6(5)
C(2)–C(1)–C(7)	120.7(5)	120.8(5)
C(2)–C(1)–C(6)	118.8(5)	119.6(5)
C(1)–C(2)–C(3)	120.6(5)	119.5(6)
C(2)–C(3)–C(4)	119.7(6)	120.8(7)
C(3)–C(4)–C(5)	120.7(6)	120.1(7)
C(4)–C(5)–C(6)	118.9(6)	120.5(7)
C(1)–C(6)–C(5)	121.3(6)	119.5(6)
C(1)–C(7)–C(8)	111.9(4)	109.0(4)
C(1)–C(7)–O(71)	108.9(4)	112.8(4)
O(71)–C(7)–C(8)	111.5(4)	109.6(4)
C(7)–C(8)–O(82)	117.5(4)	117.7(4)
C(7)–C(8)–O(81)	117.1(4)	116.3(4)
O(81)–C(8)–O(82)	125.4(5)	126.0(4)
C(9)–N–C(12)	106.7(4)	104.8(4)
N–C(9)–C(13)	111.6(4)	111.1(4)
N–C(9)–C(10)	103.9(4)	105.5(4)
C(10)–C(9)–C(13)	115.8(5)	115.6(4)
C(9)–C(10)–C(11)	104.9(6)	105.7(5)
C(10)–C(11)–C(12)	112.2(7)	106.5(6)
N–C(12)–C(11)	102.5(6)	100.9(5)
C(11)–C(12)–C(16)	114.1(6)	115.7(6)
N–C(12)–C(16)	111.5(5)	111.6(5)
C(9)–C(13)–C(15)	110.0(5)	111.1(4)
C(9)–C(13)–C(14)	108.9(5)	108.4(5)
C(9)–C(13)–O(13)	108.9(4)	109.4(5)
C(14)–C(13)–C(15)	113.0(5)	112.7(5)
O(13)–C(13)–C(15)	106.2(5)	105.8(5)
O(13)–C(13)–C(14)	109.8(4)	109.4(4)

addition of an excess (104 g) of a 1:1 mixture (by volume) of sodium sulphate decahydrate and Celite. The slurry was left overnight at room temperature whereupon it was filtered and the clear filtrate concentrated to yield crude **6** (13.2 g, GLC purity 68.6%, *cis/trans* = 76/24) as a yellow oil. The diol **6** (12.5 g of the crude material) was then dissolved in  $\text{CH}_2\text{Cl}_2$  (200 ml) and cooled to  $0^\circ\text{C}$  under  $\text{N}_2$ .  $\text{Et}_3\text{N}$  (8.4 ml, 60.2 mmol) and  $\text{MsCl}$  (4.3 ml, 55.2 mmol) were added in sequence via syringe and the reaction was stirred for 1 h at  $0^\circ\text{C}$ . Ice-water (50 ml) and aqueous  $\text{NaHCO}_3$  (sat., 50 ml) were added and the phases were separated. Further extraction of the organic phase with  $\text{H}_2\text{O}$  (100 ml) and  $\text{NaCl}$  (aq. sat., 50 ml) followed by drying ( $\text{MgSO}_4$ ), filtration and concentration gave crude **7** (13.6 g, GLC purity 47.3%, no *trans* isomer detected) as a brown oil. A solution of this material in tetrahydrofuran (THF, 300 ml) was added to a slurry of  $\text{LiAlH}_4$  (5.5 g, 144 mmol) in THF (100 ml) at  $0^\circ\text{C}$  under  $\text{N}_2$ . The reaction was stirred at room temperature (2.5 h) and then cautiously quenched with an excess of sodium sulphate decahydrate and Celite<sup>12</sup> (cf. above). After continued stirring overnight, the yellowish light grey suspension was filtered and washed with additional THF (150 ml). Concentration of the filtrate *in vacuo* gave crude **8** (10.3 g, GLC purity 36.1%). Final purification by liquid chromatography (Merck Kieselgel 60, 40–60  $\mu\text{m}$ ; gradient elution with hexane/ethyl acetate) furnished pure **8** (1.44 g, 30% overall yield based on *cis*-**4**), b.p.  $106\text{--}109^\circ\text{C}/0.32\text{ mmHg}$ .  $^1\text{H NMR}$ :  $\delta$  0.89 (3 H, d,  $\text{CH}_3$ ), 1.15 (3 H, s,  $\text{CH}_3$ ), 1.18 (3 H, s,  $\text{CH}_3$ ), 1.30–1.50 [1 H, m, C–CH(H)–C], 1.60–1.95 [3 H, m, C–C(H)H–C + C–CH<sub>2</sub>–C], 2.73 (1 H, br s, OH), 2.80–3.00 (2 H, m, NCH), 3.78 [1 H, d,  $J = 14\text{ Hz}$ , N–CH(H)– $\text{C}_6\text{H}_5$ ], 4.04 [1 H, d,  $J = 14\text{ Hz}$ , N–C(H)H– $\text{C}_6\text{H}_5$ ], 7.15–7.40 (5 H, m,  $\text{C}_6\text{H}_5$ ). Anal.  $\text{C}_{15}\text{H}_{22}\text{NO}$ : C, H, N.

*cis*-2-(1-Hydroxy-1-methylethyl)-5-methylpyrrolidine (**3**). The aminol **8** (2.0 g, 8.6 mmol) in methanol (50 ml) and  $\text{Pd/C}$ -catalyst (10%, 0.4 g) were stirred at room temperature in a 100 ml round-bottomed flask fitted with a simple

Table 4. List and dimensions of possible hydrogen bonds (a) and selected distances and angles within the hydrogen bonding scheme (b) in the crystal structure of (–)-*cis*-2-(1-hydroxy-1-methyl)-5-methylpyrrolidinium (*S*)-mandelate. The e.s.d.'s, where given,<sup>a</sup> are in parentheses.

(a)

Atoms involved	Distance/Å			Angle/ <sup>o</sup>
	Donor...Acceptor	Donor–H	H...Acceptor	Donor–H...Acceptor
O(71)–H(71)...O(82)	2.654(6)	0.96	1.94	130
N–H(N1)...O(81)	2.660(5)	0.95	1.72	172
N–H(N2)...O(82')	2.878(5)	0.92	2.06	148
O(71')–H(71')...O(13)	2.733(5)	0.97	1.99	132
O(71')–H(71')...O(82')	2.704(4)	0.97	2.06	122
N'–H(N1')...O(81')	2.656(5)	0.99	1.67	173
O(71)–H(71)...O(13') <sup>b</sup>	2.738(5)	0.96	2.09	123
O(13)–H(13)...O(71) <sup>c</sup>	2.722(5)	1.02	1.78	152
N'–H(N2')...O(82) <sup>d</sup>	2.872(5)	0.91	2.03	154
O(13')–H(13')...O(71') <sup>e</sup>	2.736(4)	0.89	1.95	147

(b)

Atoms involved			Distance/Å			Angle/ <sup>o</sup>
A	B	C	A...B	B...C	A...C	A...B...C
O(82)	...O(71)	...O(13') <sup>b</sup>	2.654(6)	2.738(5)	3.226(5)	73.5(2)
O(82')	...O(71')	...O(13)	2.704(3)	2.733(5)	3.238(4)	73.1(2)
O(82)	...H(71)	...O(13') <sup>b</sup>	1.94	2.09	3.226(5)	106
O(82')	...H(71')	...O(13)	2.06	1.99	3.238(4)	106
O(71)	...O(82)	...N' <sup>d</sup>	2.654(6)	2.872(5)	4.371(6)	104.5(2)
O(71')	...O(82')	...N	2.704(3)	2.878(5)	4.427(5)	104.9(2)
H(71)	...O(82)	...H(N2') <sup>d</sup>	1.94	2.03	2.65	84
H(71')	...O(82')	...N(N2)	2.06	2.06	2.68	81

<sup>a</sup>The H-atom positions are not refined (cf. the text). Symmetry codes: <sup>b</sup> $x+1, y, z$ ; <sup>c</sup> $-x-1/2, -y, z+1/2$ ; <sup>d</sup> $x-1, y, z$ ; <sup>e</sup> $-x-1/2-1, -y, z-1/2$ .

hydrogenation head connected to a small hydrogen balloon. The flask was repeatedly evacuated and filled with argon, and then finally with H<sub>2</sub>. Hydrogenation was complete within 6 h (GLC). The solution was filtered, concentrated and purified by Kugelrohr distillation to give **3** (0.88 g, 71 % yield) as a clear, colourless oil, b.p. 45–50°C/0.4 mmHg, <sup>1</sup>H NMR: δ 1.09–1.14 (9 H, d+s+s, 3×CH<sub>3</sub>), 1.20–1.40 [1 H, m, C–CH(H)–C], 1.60–1.90 [3 H, m, C–C(H)H–C=C–CH<sub>2</sub>–C], 3.03 (1 H, dd unres., N–CH–COH), 3.15–3.35 (1 H, m, N–CHCH<sub>3</sub>). Anal. C<sub>8</sub>H<sub>17</sub>NO: C, H, N.

**Resolution of compound 3.** Compound **3** in acetone gave with (*S*)-(+)-mandelic acid a 1:1 salt (<sup>1</sup>H NMR), m.p. 153.5–155.5°C, [α]<sub>D</sub><sup>21</sup> = +41.9° (*c* 1.385, MeOH). Anal. C<sub>16</sub>H<sub>25</sub>NO<sub>4</sub>: C, H, N. The aminol **3** and (*R*)-(–)-mandelic acid yielded the antipode of this salt, [α]<sub>D</sub><sup>21</sup> = –42.0° (*c* 1.640, MeOH). To liberate optically pure **3**, each salt was dissolved in a small amount of 1 M aq. NaOH. Extraction with diethyl ether (×6), concentration and distillation gave 90 % isolated yield of (–)-**3**, [α]<sub>D</sub><sup>21</sup> = –19.9° (*c* 1.180, CHCl<sub>3</sub>) and of (+)-**3**, [α]<sub>D</sub><sup>21</sup> = +19.2° (*c* 1.343, CHCl<sub>3</sub>) from the (+)- and (–)-mandelate, respectively. The structure determination of the (*S*)-(+)-mandelate salt by X-ray dif-

fraction shows that (–)-**3** is (2*S*, 5*S*)-*cis*-2-(1-hydroxy-1-methylethyl)-5-methylpyrrolidine.

**Crystallography. Data collection and processing.** Crystals of the title salt (C<sub>16</sub>H<sub>25</sub>NO<sub>4</sub>, *M*<sub>w</sub> = 295.378, *D*<sub>c,x-ray</sub> = 1.189 g cm<sup>–3</sup>), suitable for X-ray study, were grown from acetone solution.

Intensity data were obtained from a colourless single crystal with the approximate dimensions 0.53×0.32×0.19 mm. 3335 unique reflections were collected with Cu *K*<sub>α</sub> radiation (λ = 1.5418 Å, θ<sub>max</sub> = 70°) at room temperature on a Siemens STOE/AED2 diffractometer equipped with a graphite monochromator, using the ω–2θ scan technique. Data reduction included corrections for background, Lorentz and polarization effects, but the relatively low absorption effects (μ = 6.55 cm<sup>–1</sup>) were ignored.

The orthorhombic unit cell with the space group symmetry *P*2<sub>1</sub>2<sub>1</sub> has *a* = 9.622(1), *b* = 16.707(1), *c* = 20.529(2) Å, *V*<sub>c</sub> = 3300.1(3) Å<sup>3</sup> and *Z* = 8. The cell parameters were refined against Θ values of 42 well-centred strong reflections, measured on the diffractometer within the range 43° < 2θ < 81°.

*Solution and refinement of the structure.* Direct method calculations (SHELXS<sup>13</sup>) resulted in an initial structural model comprising all the non-hydrogen atoms of the two formula units. This model was then refined by full-matrix least-squares treatments based upon  $|F|$  (SHELX<sup>14</sup>). The nitrogen- and oxygen-bonded H atoms were located from difference electron-density maps and were held riding on their respective mother atoms during the subsequent calculations, while the carbon-bonded hydrogens were given geometrically assumed positions, recalculated after each cycle of the refinement. The methyl groups were treated as rigid groups with free rotation around the C–C bond.

In the final stage of the refinement, the non-hydrogen atomic positions were refined with their anisotropic thermal parameters while isotropic temperature factors were refined for the hydrogen positions: four common (= group) isotropic temperature factors for the calculated H atoms of the four ionic moieties and individual factors for the *N*- and *O*-bonded hydrogens. Three strong low- $\theta$  reflections (2 0 0, 0 2 0, and 1 0 4), with considerably higher  $|F_{\text{calc}}|$  than  $|F_{\text{obs}}|$ , probably due to extinction effects, were excluded from the final calculations, in which the refinement of 411 variables converged to a linear *R* value of 0.051 for 2425 reflections, all with  $F > 6\sigma(F)$ . The weighted *R* reached the value of  $R_w = [\sum w|\Delta F|^2 / \sum w|F_o|^2]^{1/2} = 0.055$ . The weights of the structure factors were estimated to be  $w = 5.8036/[\sigma^2(F) + 0.00002F^2]$ . The atomic scattering factors for the C, O and N atoms were taken from Cromer and Mann,<sup>15</sup> and those for the H atoms from Stewart *et al.*<sup>16</sup> The corrections for the anomalous dispersion of the non-hydrogen atoms were taken from Cromer and Liberman.<sup>17</sup>

The two chiral centres in the pyrrolidine ring, C(9) and C(12) [cf. Fig. 1], both proved to have the *S* configuration in the present crystal structure. This could be deduced directly from the X-ray results, as the configuration of the mandelate moiety is known.<sup>7</sup> Table 1 lists the final atomic coordinates, which refer to the correct enantiomer.

Lists of the coordinates and isotropic temperature factors for the calculated hydrogen atoms are deposited with the Cambridge Crystallographic Data Centre (University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England). Lists of the anisotropic thermal parameters of the non-hydrogen atoms, and of the observed and calculated structure factors, as well as the list of the calculated hydrogen positions are available directly from I. C. upon request.

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## References

- See for example: (a) Enders, D. *Chem. Scr.* 25 (1985) 139; (b) Kawanami, Y., Ito, Y., Kitagawa, T., Katsuki, T. and Yamaguchi, M. *Tetrahedron Lett.* 25 (1984) 857; (c) Mukaiyama, T. *Chem. Scr.* 25 (1985) 13; (d) Soai, K., Ookawa, A., Kaba, T. and Ogawa, K. *J. Am. Chem. Soc.* 109 (1987) 7111; (e) Takano, S., Moriya, M., Iwabuchi, Y. and Ogasawara, K. *Tetrahedron Lett.* 30 (1989) 3805.
- Schlessinger, R. H. and Iwanowicz, E. J. *Tetrahedron Lett.* 28 (1987) 2083.
- (a) Lin Guoqiang, Hjalmarsson, M., Högberg, H.-E., Jernstedt, K. and Norin, T. *Acta Chem. Scand., Ser. B* 38 (1984) 795; (b) Hjalmarsson, M. and Högberg, H.-E. *Acta Chem. Scand., Ser. B* 39 (1985) 793.
- Dahlén, E., Hjalmarsson, M. and Norin, T. *To be published.*
- Cignarella, G. and Nathansohn, G. *J. Org. Chem.* 26 (1961) 1500.
- Boutelje, J., Hjalmarsson, M., Hult, K., Lindbäck, M. and Norin, T. *Bioorganic Chem.* 16 (1988) 364.
- Liu, Ling-Kang and Davis, R. E. *Acta Crystallogr., Sect. B* 36 (1980) 171.
- Cremer, D. and Pople, J. A. *J. Am. Chem. Soc.* 97 (1975) 1354.
- Klyne, W. and Prelog, W. *Experientia* 16 (1960) 521.
- Stanford, R. H., Jr. and Waser, J. *Acta Crystallogr., Sect. A* 28 (1972) 213.
- Crude **5** contains a by-product which is less soluble in diethyl ether and has preliminarily been identified as *meso-trans-N*-benzyl-2,5-bis-(1-hydroxy-1-methylethyl)pyrrolidine, m.p. 114–115°C. <sup>1</sup>H NMR:  $\delta$  1.09 (6 H, s, 2×CH<sub>3</sub>), 1.17 (6 H, s, 2'CH<sub>3</sub>), 1.60–2.05 (4 H, m, C–CH<sub>2</sub>–C), 2.90–3.00 (2 H, m, NCH), 3.08 (2 H, s, OH), 3.93 (2 H, s, NCH<sub>2</sub>), 7.15–7.55 (5 H, m, Ph).
- Baekström, P. *Tetrahedron* 34 (1978) 3331.
- Sheldrick, G. M. SHELXS 84: Program for Crystal Structure Solution, University of Göttingen, FR-Germany 1984. *Personal communication.*
- Sheldrick, G. M. SHELX 400 ATOMS VERSION: updated by D. Rabinovich and K. Reich, Department of Structural Chemistry, Weizmann Institute of Science, Rehovot, Israel; and subsequently modified by G. M. Sheldrick, University of Göttingen, FR-Germany 1979. *Personal communication.*
- Cromer, D. T. and Mann, J. B. *Acta Crystallogr., Sect. A* 24 (1968) 321.
- Stewart, R. F., Davidson, E. R. and Simpson, W. T. *J. Chem. Phys.* 42 (1965) 3175.
- Cromer, D. T. and Liberman, D. *J. Chem. Phys.* 53 (1970) 1891.

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