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TETRAHEDRON: *ASYMMETRY*

Synthesis, absolute configuration and intermediates of 9-fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (flumequine)

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Abstract

The antibacterial agent 9-fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (flumequine) was synthesized in optically active form from 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ). Racemic FTHQ was resolved with the enantiomers of 3-bromocamphor-8-sulfonic acid. The configurations were established by X-ray structures of the two diastereoisomeric salts. Enantiomeric excesses were determined by ^{1}H NMR analysis.

1. Introduction

9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (flumequine, **4**, Fig. 1) is an antibacterial agent, having a significant difference between the effectiveness of the two enantiomers. Thus, a convenient and cost-effective method for preparing the isomers is of interest.

One method is described in the literature: Rohlfing et al. performed the optical resolution of the intermediate 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ, **1**) by separating its enantiomers via

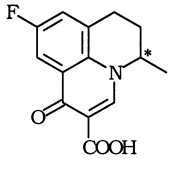

Figure 1. 9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (flumequine, **4**)

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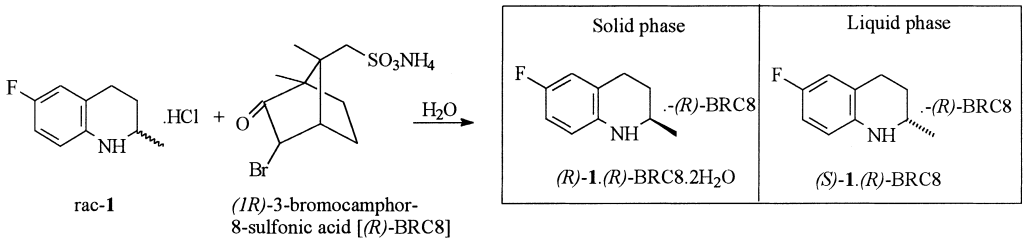
their diastereoisomeric amides of *N*-tosyl-(*S*)-proline[1] and synthesized optically active flumequine from optically active FTHQ. However, this method involves covalently bonded diastereoisomers, which makes the process impractical and complicated. Here we report our results on the resolution of FTHQ using a simple diastereoisomeric salt formation method.

2. Results and discussion

Having failed to separate the enantiomers of racemic flumequine we focused on resolving the FTHQ intermediate and manufacturing optically active flumequine from it. 2-Methyl-1,2,3,4-tetrahydroquinoline and 2,6-dimethyl-1,2,3,4-tetrahydroquinoline have previously been resolved by 3-bromocamphor-8-sulfonic acid.[2,3] This fact, based on the observation that similar molecules can often be resolved with the same resolution agent,[4] prompted us to try this resolving agent first. The 3-bromocamphor-8-sulfonic acid enantiomers proved to be adequate when applied in a molar ratio of 1:1 [represented on the example of the (*R*)-isomer, Scheme 1].



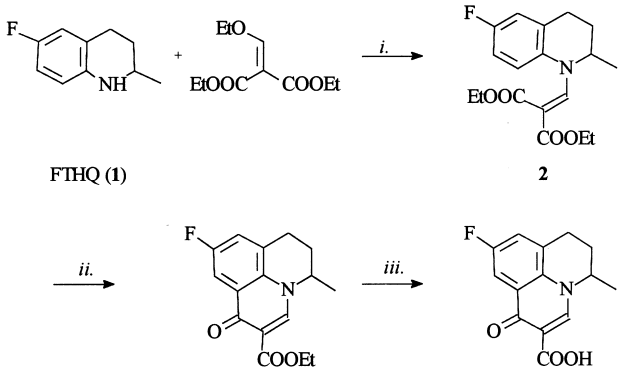
Scheme 1. Resolution of FTHQ (*rac*-**1**)

Racemic FTHQ was dissolved in hot hydrochloric acid solution and the resolution agent was added as its ammonium salt. Hydrochloric acid excess was necessary to prevent dissociation of the weakly basic FTHQ. The crystalline phase was enriched in the (*R*)-**1**·(*R*)-BRC8, and the mother liquor in the (*S*)-**1**·(*R*)-BRC8 diastereoisomeric salt. The solid diastereoisomeric salt gave enantiomerically pure (*R*)-**1** after cleavage following two recrystallization steps from 5% HCl solution. Enantiomerically pure (*S*)-**1** was obtained using (1*S*)-3-bromocamphor-8-sulfonic acid as described above.

For production of racemic flumequine from racemic FTHQ, the following method[5] was applied (Scheme 2).

We carried out the above reaction route starting from both the racemate and enantiomerically pure **1**. The results are summarized in Table 1. As the reactions do not affect the stereogenic centre, (*R*)-flumequine can be obtained from (*R*)-FTHQ essentially without racemization. Similarly, (*S*)-FTHQ gives (*S*)-flumequine.

X-Ray crystallography established the absolute configurations of both *S*-**1**·(*R*)-BRC8 and *R*-**1**·(*R*)-BRC8 salts (Figs. 2 and 3). In addition, it has also revealed the possible structural basis of the successful resolution of racemic FTHQ with 3-bromocamphor-8-sulfonic acid. The structure of *S*-**1**·(*R*)-BRC8 is hydrogen bond donor deficient. The ratio of the hydrogens to acceptor pairs is 2:8. The hydrogen bonds form endless chains travelling through the crystal structure (Fig. 4). Only two of the oxygens of the SO_3^- group are able to participate in hydrogen bonds and the hydrogen bond chains are based on $HNH^+ \ldots OSO_2^- \ldots HNH^+ \ldots OSO_2^-$ repeating units. These hydrogen bond chains are not interconnected. The carbonyl group of the camphorsulfonic acid is deeply embedded in a hydrophobic layer of the crystal structure.



i. 110-115°C; *ii.* Polyphosphoric acid, 100-110°C in toluene; *iii.* H_2O/H^+

Scheme 2. Synthesis of racemic flumequine

Table 1
Synthesis of flumequine from FTHQ (racemic and optically active routes)

Compound	Abs. config.	$[\alpha]_D^{20}$	ee [a] %	Y [d] %	mp [d] °C
1	*(R)* [e]	+70.2 (c=1, ethanol)	>98[b]	-	40-43
2	*(R)* [f]	-266.1 (c=1, ethanol) -288.1 (c=1, DMF)	-[c]	96.1	oil
3	*(R)* [f]	+81.5 (c=1, ethanol) +73.9 (c=1, DMF)	-[c]	80.5	188-190
4	*(R)* [f]	+48.9 (c=0.21, DMF)	>98[b]	75.4	247-250
1	*racemic*	-	-	-	34-36
2	*racemic*	-	-	97.0	oil
3	*racemic*	-	-	69.1	183-186
4	*racemic*	-	-	70.8	256-259
1	*(S)*	-70.0 (c=1, ethanol)	>98[b]	-	40-42
2	*(S)*	+264.7 (c=1, ethanol) +287.9 (c=1, DMF)	-[c]	97.0	oil
3	*(S)*	-81.5 (c=1, ethanol) -73.4 (c=1, DMF)	-[c]	81.9	187-189
4	*(S)*	-48.6 (c=0.21, DMF)	>98[b]	77.5	246-249

[a] Enantiomeric excess was determined by NMR method: 6.3 equivalent of *(R)*-(-)-(9-anthryl)-2,2,2-trifluoroethanol as chiral solvating agent was applied; [b] No peak of the other enantiomer was detected; [c] Not determined; [d] The data (except for compound **2**) refer to products purified by recrystallization; [e] Determined by X-ray crystallography (see next section); [f] derived from the absolute configuration of compound **1**.

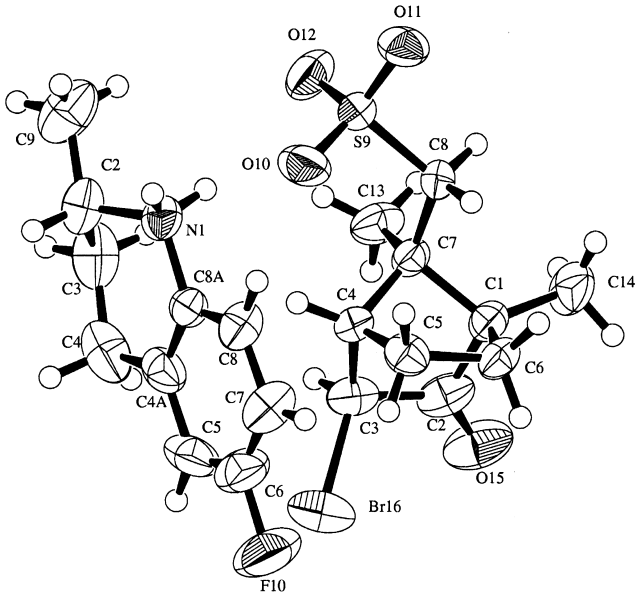


Figure 2. Structure of the ion pair as found in the crystal of *S*-**1**·(*R*)-BRC8

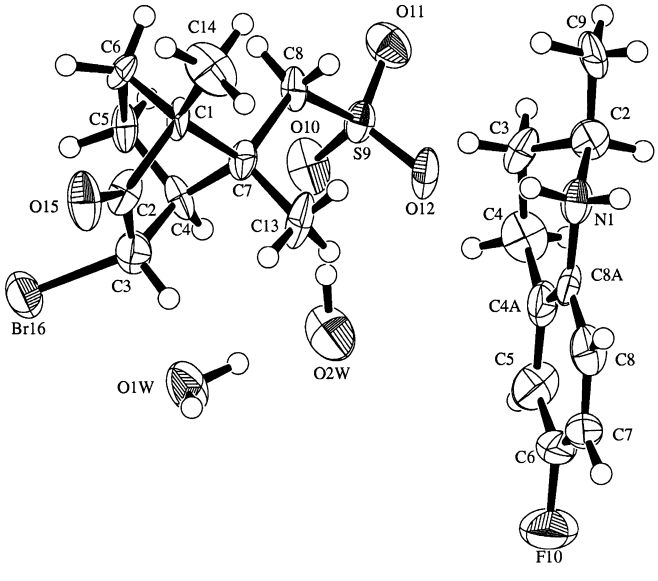


Figure 3. Structure of the ion pair as found in the crystal of *R*-**1**·(*R*)-BRC8

On the contrary, in *R*-**1**·(*R*)-BRC8 two water molecules are also included in the crystal lattice. The ratio of acidic hydrogens to acceptor pairs is only 6:12. Each oxygen of the SO_3^- groups participates in hydrogen bonding. The hydrogen bonds form two-dimensional networks utilizing the two water molecules (as mediators) as well as all three oxygen atoms of the sulfonate moiety. In addition, the carbonyl group of the camphorsulfonate is also involved in the hydrogen bond network since one of the water molecules sinks deeply into the hydrophobic layer to form a hydrogen bond with that carbonyl group (Fig. 5). The more extended hydrogen bond network — which is due to the presence of two additional water molecules — is probably responsible for the higher stability of the *R*-**1**·(*R*)-BRC8 salt.

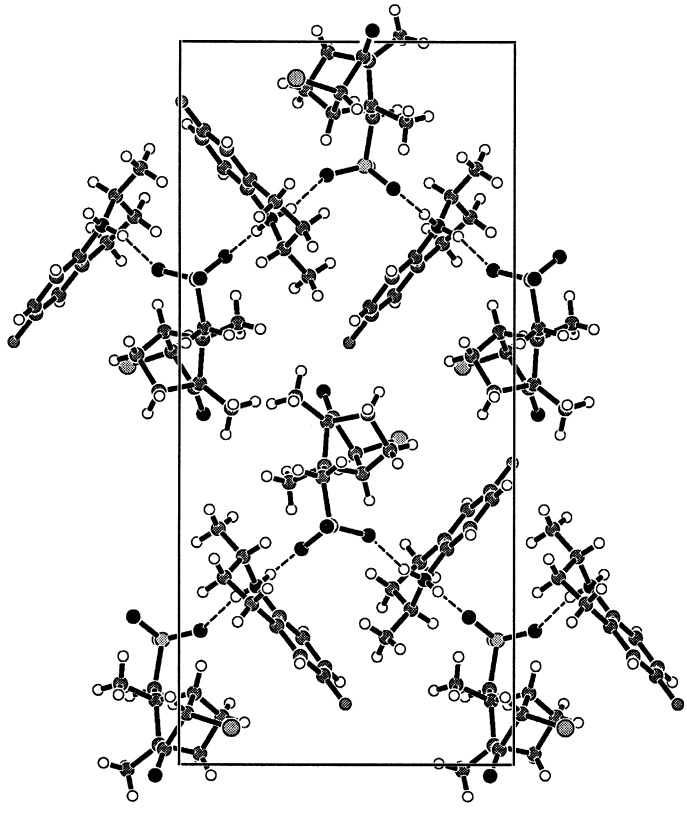


Figure 4. Crystal packing diagram of *S*-**1**·(*R*)-BRC8

3. Experimental

3.1. Materials and methods

The ^{1}H NMR spectra were recorded at 500 MHz on a Bruker DRX-500 spectrometer. Chemical shift values are expressed in ppm values on the δ scale. IR spectra of thin film samples were taken on a Specord 2000 spectrometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. (*S*)- and (*R*)-3-Bromocamphor-8-sulfonic acid ammonium salts were purchased from Aldrich. FTHQ was manufactured in Chinoin. All solvents were freshly distilled.

*3.2. Preparation of **2** from FTHQ*

Racemic FTHQ (1.0 g, 6.05 mmol, mp 34–36°C) was stirred with diethylethoxymethylene malonate (1.3 g, 6.01 mmol) at 125°C for 2.5 h. The mixture was kept at this temperature in vacuo for 1 h to yield a brownish yellow, viscous oil (1.97 g, 5.87 mmol, 97.0%).

The same reaction starting from (*S*)-FTHQ ($[\alpha]_D$=−70.0, *c*=1, ethanol) yielded brownish yellow viscous oil (97.0%, $[\alpha]_D$=+264.7, *c*=1, ethanol; +287.9, *c*=1, dimethyl formamide).

The same reaction starting from (*R*)-FTHQ ($[\alpha]_D$=+70.2, *c*=1 ethanol) yielded brownish yellow viscous oil (96.1%, $[\alpha]_D$=−266.1, *c*=1, ethanol; −288.1, *c*=1, dimethyl formamide).

^{1}H NMR: ($CDCl_3$): 1.21 (d, 3H, CH_3), 1.28 (m, 6H, CH_3–Et), 1.7–2.1 (ms, 2H, CH_2), 2.7–2.9 (ms, 2H, Ar–CH_2), 4.0–4.3 (ms, 5H, 2CH_2–E+CH), 6.8–7.0 (m, 3H, Ar), 7.7 (s, 1H, =CH). FT-IR (film,

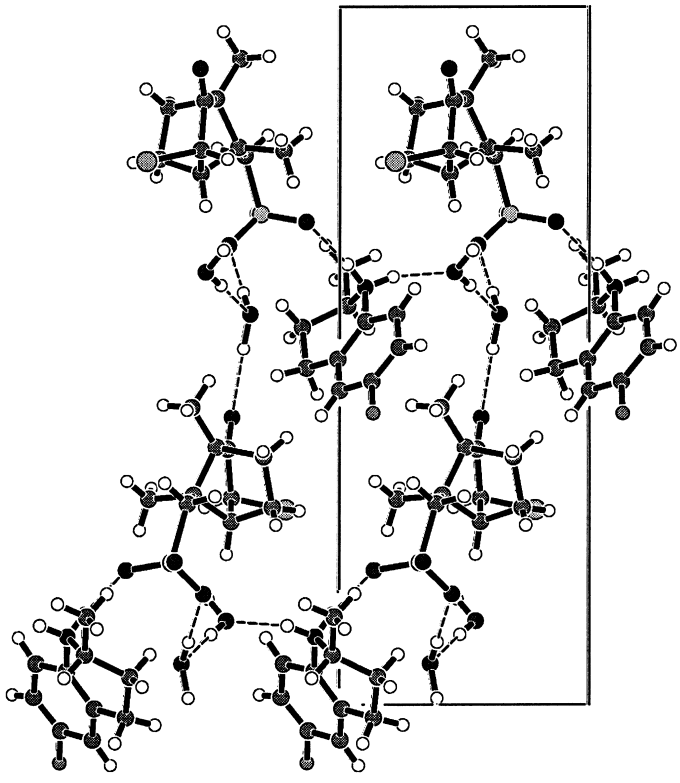


Figure 5. Crystal packing diagram of *R*-**1**c·(*R*)-BRC8

cm^{-1}): 3398, 2981, 2937, 2499, 1695, 1593, 1499, 1438, 1382, 1364, 1291, 1267, 1243, 1227, 1192, 1074, 1045, 1027, 951, 919, 873, 812, 663. Calcd for $C_{18}H_{22}NO_4F$: C, 64.46; H, 6.61; N, 4.18; found C, 64.27; H, 6.60; N, 4.20.

NMR and IR spectra are identical for the racemic and optically active **2**.

*3.3. Preparation of flumequine ethyl ester **3***

Racemic FTHQ (2.0 g, 12.1 mmol, mp 34–36°C) was stirred with diethylethoxymethylene malonate (3.0 g, 13.9 mmol) at 125°C for 2.5 h. The mixture was kept at this temperature in vacuo (10 mmHg) for 30 min. After cooling, polyphosphoric acid (3.0 g) was added and the mixture was stirred at 110°C for 6 h. After this time, the reaction mixture was poured into water (50 ml) and left to stand for 4–5 h. After filtration, washing with water (5×10 ml) and drying, 2.98 g of off-white powder was obtained. After recrystallizing from ethanol, white powder (2.42 g, 8.37 mmol, 69.1%, mp 183–186°C) was obtained.

The same reaction starting from (*S*)-FTHQ ($[\alpha]_D$=−70.0, *c*=1, ethanol) yielded white powder (81.9%, $[\alpha]_D$=−81.5, *c*=1, ethanol; −73.4, *c*=1, dimethyl formamide, mp 187–189°C).

The same reaction starting from (*R*)-FTHQ ($[\alpha]_D$=+70.2, *c*=1, ethanol) yielded white powder (80.5%, $[\alpha]_D$=+81.5, *c*=1, ethanol; +73.9, *c*=1, dimethyl formamide, mp 188–190°C).

^{1}H NMR: ($CDCl_3$): 1.41 (t, 3H, CH_3–Et), 1.49 (d, 3H, CH_3), 2.1–2.3 (m, 2H, CH_2), 3.0–3.2 (ms, 2H, Ar–CH_2), 4.4 (q, 2H, CH_2–Et), 4.5 (m, 1H, CH), 7.2–8.0 (m, 2H, Ar), 8.4 (s, 1H, =CH). FT-IR (KBr, cm^{-1}): 3420, 2991, 1719, 1623, 1593, 1565, 1486, 1428, 1414, 1311, 1219, 1166, 1136, 1103, 1048, 915, 878, 804, 740, 627. Calcd for $C_{16}H_{16}NO_3F$: C, 66.43; H, 5.57; N, 4.84; found C, 66.23; H, 5.59; N, 4.82.

NMR and IR spectra are identical for the racemic and optically active **3**.

3.4. Preparation of flumequine **4**

Racemic FTHQ (2.0 g, 12.1 mmol, mp 34–36°C) was stirred with diethylethoxymethylene malonate (3.0 g, 13.9 mmol) at 125°C for 2.5 h. The mixture was kept at this temperature in vacuo (10 mmHg) for 30 min. After cooling, polyphosphoric acid (3.0 g) was added and the mixture was stirred at 110°C for 6 h. After adding water (6 ml), it was stirred at 100°C for 3 h and then 1 h at 0°C, then filtered. The cake was washed with water (5×2 ml), ethanol (3×1 ml) and was dried to yield 2.47 g of yellowish material, which was then dissolved in hot dimethyl formamide (5 ml), cooled to 0–3°C, filtered, washed with dimethyl formamide (2×0.5 ml), water (3×2 ml), ethanol (2×1 ml) and dried to yield white crystals (2.24 g, 8.57 mmol, 70.8%, mp 256–259°C).

The same reaction starting from (*S*)-FTHQ ($[\alpha]_D$=−70.0, *c*=1 ethanol, mp 40–42°C) yielded white crystals (77.5%, $[\alpha]_D$=−48.6, *c*=0.21, dimethyl formamide, mp 246–249°C).

The same reaction starting from (*R*)-FTHQ ($[\alpha]_D$=+70.2, *c*=1, ethanol, mp 40–43°C) yielded white crystals (75.4%, $[\alpha]_D$=+48.9, *c*=0.21, dimethyl formamide, mp 247–250°C).

^{1}H NMR: ($CDCl_3$): 1.55 (d, 3H, CH_3), 2.2–2.3 (m, 2H, CH_2), 3.0–3.2 (m, 2H, Ar–CH_2), 4.6 (m, 1H, CH), 7.3–8.0 (m, 2H, Ar), 8.7 (s, 1H, =CH), 14.9 (s, 1H, COOH). FT-IR (KBr, cm^{-1}): 3448, 3055, 2990, 2723, 1724, 1621, 1567, 1518, 1471, 1423, 1394, 1376, 1340, 1318, 1303, 1272, 1212, 1196, 1134, 1067, 974, 899, 886, 810, 719, 698, 646. Calcd for $C_{14}H_{12}NO_3F$: C, 64.36; H, 4.63; N, 5.36; found C, 64.55; H, 4.64; N, 5.36.

NMR and IR spectra are identical for the racemic and optically active **4**.

3.5. Optical resolution of FTHQ **1**

Racemic FTHQ (2.0 g, 12.1 mmol) and (*R*)-3-bromocamphor-8-sulfonic acid ammonium salt (4.0 g, 12.2 mmol) were dissolved in hot hydrochloric acid solution (1.5 ml of concentrated hydrochloric acid and 20 ml of water). The mixture was cooled to room temperature. Crystallization was initiated by scratching. After standing at room temperature with occasional stirring for 1 h it was filtered. The diastereoisomeric salt was recrystallized twice from 5% hydrochloric acid solution (5 ml). After filtration and drying, white crystalline material was obtained (1.71 g, $[\alpha]_D$=+86.3, *c*=1, methanol, mp 169–172°C).

Ethyl acetate (20 ml) was added and the mixture was washed with 1 M Na_2CO_3 (3×10 ml). The organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo to yield white crystals (0.52 g, $[\alpha]_D$=+70.0, *c*=1, ethanol, mp 40–42°C).

For the mother liquor, ethyl acetate (20 ml) was added and the mixture was washed with 1 M Na_2CO_3 (3×30 ml). The organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo to yield an oily-crystalline material (1.10 g, $[\alpha]_D$=−33.4, *c*=1, ethanol).

The other enantiomer of FTHQ was obtained similarly with the enantiomer from the resolving agent.

3.6. X-Ray crystallography

Crystals were obtained as follows.

(*S*)-(−)-FTHQ (0.20 g, 1.21 mmol, $[\alpha]_D^{20}$=−70, *c*=1, ethanol) and (*R*)-3-bromocamphor-8-sulfonic acid monohydrate (0.42 g, 1.27 mmol) were dissolved in hot water (5 ml). The solution was cooled to room temperature, inoculated and left to crystallize overnight. The crystals were filtered and air-

Table 2
Crystal data and experimental details

	S-**1**.*(R)*-BRC8.	*R*-**1**.*(R)*-BRC8
Empirical formula	$C_{20}H_{27}BrFNO_4S$	$C_{20}H_{31}BrFNO_6S$
Formula weight	476.40	512.43
Temperature	293(2) K	
Wavelength	1.54178 A	
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
Unit cell dimensions	a = 11.801(6) Å	7.532(6) Å
	b = 25.278(8) Å	20.561(2) Å
	c = 7.232(4) Å	7.6697(14) Å
	β =	105.09(5) deg.
Volume	2157(2) $Å^3$	1146.8(10) A^3
Z	4	2
Density (calculated)	1.467 Mg/m^3	1.484 Mg/m^3
Absorption coefficient	3.796 mm^{-1}	3.677 mm^{-1}
F(000)	984	532
Crystal size	1.00x0.30x0.20mm	0.50x0.10x 0.10mm
Theta range for data collection	3.50 to 75.10 deg.	4.30 to 75.16 deg.
Index ranges	-6 <=h<=14,	-8<=h<=9,
	-12<=k<=31,	-25<=k<=25,
	-9 <=l<=8	-9<=l<=9
Reflections collected	2542	2486
Independent reflections	2542	2339 [R(int)=0.124]
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2541 / 0 / 258	2338 / 1 / 279
Goodness-of-fit on F^2	1.039	0.977
Final R indices [I>2sigma(I)]	R1 = 0.0661	0.1190
	wR2 = 0.1696	0.3042
R indices (all data)	R1 = 0.0908	0.1566
	wR2 = 0.2054	0.3718
Absolute structure parameter	0.18(6)	-0.07(10)
Extinction coefficient	0.0076(9)	no corr.
Largest diff. peak	0.910 $e.A^{-3}$	1.855 $e.A^{-3}$
Largest diff. hole	-0.913 $e.A^{-3}$	-3.032 $e.A^{-3}$

dried to yield white needles (0.40 g), $[\alpha]_D^{20}$=+30.8 (*c*=1, methanol), mp: 178–181°C. Calcd for $C_{20}H_{27}BrFNO_4S$: C. 50.42; H, 5.71; N, 2.94; found C, 50.31; H, 5.72; N, 2.95.

(*R*)-(+)-FTHQ (0.20 g, 1.21 mmol, $[\alpha]_D^{20}$=+70.2, *c*=1, ethanol) and (*R*)-3-bromocamphor-8-sulfonic acid monohydrate (0.42 g, 1.27 mmol, $[\alpha]_{D,dry\ mat.}$=+105 to +108, *c*=1, water) were dissolved in hot water (6 ml). The solution was cooled to room temperature, inoculated and left to crystallize for 1 h. The crystals were filtered and air-dried to yield white crystals (0.46 g), $[\alpha]_D^{20}$=+86.5 (*c*=1, methanol), mp:

at 78–82°C partially dissolved in its own crystal water, above 100°C lost crystal water and finally melted at 171–174°C. Calcd for $C_{20}H_{31}BrFNO_6S$: C, 46.88; H, 6.10; N, 2.73; found C, 47.05; H, 6.12; N, 2.72.

Data were recorded at 293 K with a Rigaku AFC6S diffractometer using graphite monochromatized CuKα. Three intensity standards were measured every 150 reflections and indicated no decay during data collection. Data reduction included corrections for Lorentz and polarization effects.

The structure was solved using direct methods. Coordinates and anisotropic thermal motion parameters for all non-hydrogen atoms were refined. Hydrogen atoms were placed in calculated positions depending on the nature of the atom bonded to the hydrogen. Isotropic thermal motion parameters were refined by constraining chemically similar hydrogen atoms to obtain the same values.

The programs used for absorption corrections, data reduction, structure solution and presentation were from the TEXSAN package.[6] Refinement was performed using SHELXL-93.[7] The results are shown in Table 2.

Acknowledgements

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