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Axially chiral dilactams. Synthesis, racemization barriers and crystal structures

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Abstract

The racemic as well as optically active dilactams **1** and **2** were prepared as the first representatives of axially chiral dilactams possessing a biaryl axis as the sole element of chirality. Their absolute configurations and inversion barriers were determined. The molecular structure and supramolecular self-assembly of the racemic dilactams directed by hydrogen bonding and aryl–aryl stacking was elucidated by single crystal diffraction analysis.

1. Introduction

Chiral dilactams represent important model compounds for the design of peptide mimetics[1] and also serve as interesting tectones for the investigation of the supramolecular self-assembly directed by molecular chirality features.[2] In the course of our studies of axially chiral amino acids, their analogues and derivatives,[3–6] we have become interested in the hitherto unknown axially chiral dilactams possessing a biaryl axis as the sole element of chirality. We herewith describe the synthesis, racemization barriers and crystal structures of the isomeric dilactams **1** and **2** as the first representatives of this novel class of axially chiral compounds of C_2 symmetry.

2. Synthesis

Both the racemic and enantiomerically highly enriched dilactams (*RS*)-**1** and (*S*)-**1** were prepared from the respective diesters (*RS*)-**3** and (*S*)-**3** (Scheme 1). The reaction sequence involved bromination to

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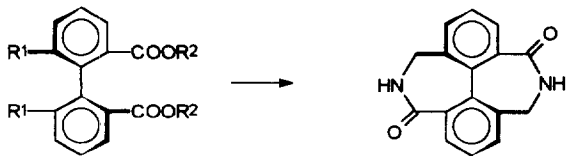
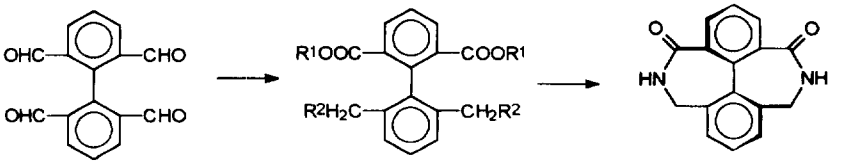
dibromo ester **4** which was converted into the diazido derivative **5**. Since purification of the dibromo ester **4** resulted in a great loss of material, the conversion of **3** into **5** was carried out with crude intermediates in the racemic as well as the enantiomerically pure series. The crude **5** was reduced with triphenylphosphine to give dihydrochloride of the diester **6**. Dilactam **1** was obtained by sodium methoxide-catalyzed cyclization of the diester **6**, liberated in situ from its dihydrochloride. Alternatively, the diazido compound **5** was reduced by hydrogenation over palladium on carbon to the free diamino ester **6** which was directly cyclized to give the dilactam **1**. Optically active dilactam (*S*)-**1** could not be purified by crystallization because the pure enantiomer was evidently much more soluble than the racemate. It showed measurable racemization at 23°C. However, as seen from the racemization experiments (*vide infra*), cyclization at 0°C should give a product of high optical purity.



(S)-**3** $R^1 = CH_3$, $R^2 = CH_3$
(S)-**4** $R^1 = CH_2Br$, $R^2 = CH_3$
(S)-**5** $R^1 = CH_2N_3$, $R^2 = CH_3$
(S)-**6** $R^1 = CH_2NH_2$, $R^2 = CH_3$

(S)-**1**



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8, $R^1 = H$, $R^2 = OH$
9, $R^1 = H$, $R^2 = Br$
10, $R^1 = CH_3$, $R^2 = Br$
11, $R^1 = CH_3$, $R^2 = N_3$
12, $R^1 = CH_3$, $R^2 = NH_2$

(S)-**2**

Scheme 1.

The isomeric dilactam **2** was synthesized starting from the tetra aldehyde **7**. Cannizzaro reaction of **7** afforded a mixture[7] of two positionally isomeric acids from which the predominant desired dihydroxy diacid **8** was obtained in a pure form by crystallization from water. The usual conversion via the dibromo and diazido derivatives **9–11** gave the diamino diester **12** which cyclized to give the dilactam **2**. Racemic (*RS*)-**2** was separated into enantiomers by preparative HPLC on triacetylcellulose in ethanol.

3. Absolute configuration

The *S*-configuration of the dextrorotatory dilactam (+)-**1** follows unambiguously from the *S*-configuration of the starting[8] diester (*S*)-**3**. On the other hand, the dilactam **2**, arising from an achiral precursor, required configurational assignment. This was done by comparing its CD spectrum with that of the dilactam (*S*)-**1**. As seen from Fig. 1, the spectra of the antipode (+)-**2** and (*S*)-**1** are very similar in wavenumbers as well as $\Delta\varepsilon$ values. Accordingly, the antipode (+)-**2** can be assigned *S*-configuration.

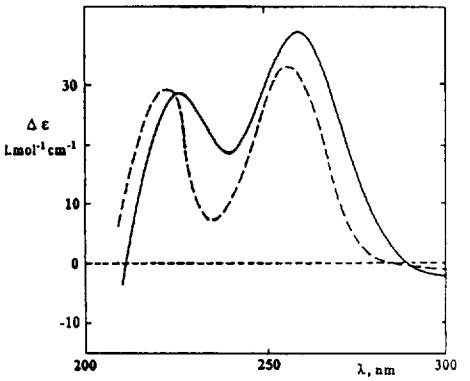


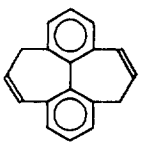
Fig. 1. CD spectra of dilactams (*S*)-**1** and (*S*)-**2** in 50% aqueous methanol (c=2.10^{-3} mol/l); (*S*)-**1** – – –, (*S*)-**2** —

Table 1
Racemization barriers in axially chiral dilactams **1** and **2** and their carbocyclic analogues **13** and **14**

Compound	1	2	13	14
Barrier (kJ/mol)	104.1	101.1	103.7	101.2

4. Inversion barriers

The inversion barriers were determined by racemization experiments. As seen from Table 1, they are very similar for both dilactams **1** and **2**. Interestingly, they are almost the same as those found[9] for the parent carbocyclic systems **13** and **14** with double bonds in place of the amide linkages, indicating thus a quasi-double bond character of the amide grouping in the systems.



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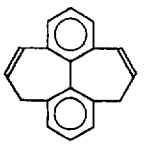

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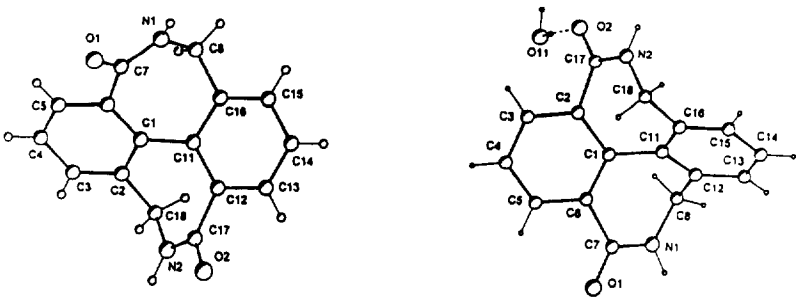
5. Molecular structures and hydrogen-bonding patterns in crystals

The molecular structures of the racemic dilactams (*RS*)-**1** and (*RS*)-**2**, as determined by single crystal X-ray diffraction, are shown in Fig. 2.

In both the isomeric dilactams, the molecular structure involves two crystallographically independent but geometrically nearly identical $-C_6H_3CONHCH_2-$ units. They are mutually oriented so as to produce dihedral angles of the mean phenyl planes which are closely similar in both the dilactams **1** and **2** [43.6(3)° and 43.1(2)°, respectively]. The aromatic rings and neighbouring amide groups remain nearly planar in both isomers. On the other hand, the pivot methylene groups are displaced from the mean aromatic plane by 0.088 Å in **1** and by as much as 0.192 Å in **2**, the molecular structure of the latter isomer being accordingly more distorted.

Self-assembly by hydrogen bonding of the axially chiral dilactams **1** and **2** raises considerable interest. According to model examination, the resulting architecture may vary in dependence on stereochemical homogeneity of the substances. Self-assembly of the homochiral dilactams **1** or **2** is expected to give rise



(*R*)-**1** (*S*)-**2**

Fig. 2. Perspective view of molecule of (*R*)-**1** and (*S*)-**2**, as obtained by X-ray diffraction of (*RS*)-**1** and (*RS*)-**2**, respectively, with atom labeling

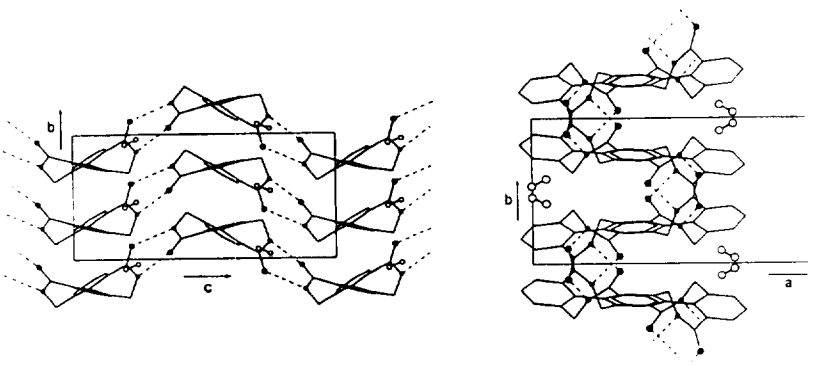


Fig. 3. Motif of supramolecular assembly of (*RS*)-**1** (two projections); intermolecular contacts drawn as dotted lines

to a helix. In the racemic dilactams, attainment of an analogous architecture would require a separate[10] self-assembly of the individual enantiomers, giving rise to a 1:1 mixture of oppositely handed helices. As another alternative, the racemic forms may lead to formation of an infinite zig-zag chain of alternating (*R*)- and (*S*)-units.

Satisfactory single crystals have so far been obtained only for the racemic dilactams **1** and **2**. Dilactam (*RS*)-**1** has been found to self-assemble by double intermolecular hydrogen bonds between carbonyl oxygens and amide hydrogens (Fig. 3), thus forming zig-zag chains of alternating (*R*)- and (*S*)-molecules. The chains run along the crystallographic *c*-direction and are further associated in the *b*-direction by a hydrophobic interaction between symmetry-related phenyl groups. These 'slipped' phenyl groups are parallel by symmetry and their mean perpendicular distance is 3.43(1) Å. When looking along the *c*-direction, it became obvious that the chains are arranged in layers (again in the zig-zag manner) but the layers are only two chains thick. Clearly, an infinite π-association of the chain through the phenyl groups at the opposite side of the molecules is prohibited by the unfavourable dihedral angle between the phenyl groups, imposed by the rigid molecular structure. Instead, the π-bonded layers are simply stacked in the *a*-direction at van der Waals distances. The solvating molecule of methanol is disordered over two positions and is clathrated without any significant intermolecular contacts.

In contrast, the solvating water molecule in dilactam (*RS*)-**2** directly participates in the self-assembly (Fig. 4). In this case, only one lactam grouping of each dilactam molecule is engaged in the double intermolecular hydrogen bonding between the carbonyl oxygens and amide hydrogens, which leads to dimers consisting of one (*R*)- and one (*S*)-molecule. The amide and carbonyl groups of the second lactam grouping are hydrogen bonded to the water molecule which links the dimers in the perpendicular

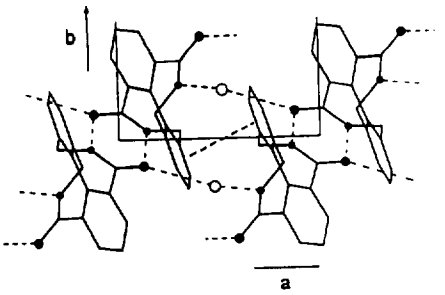


Fig. 4. Motif of supramolecular assembly of (*RS*)-**2**; intermolecular contacts drawn as dotted lines

direction. Again, there is a hydrophobic interaction between phenyl groups of adjacent dimers in which the parallel, 'slipped' phenyl groups are 3.42(2) Å apart.

6. Experimental

6.1. (RS)-Dimethyl 6,6′-bis(aminomethyl)-1,1′-biphenyl-2,2′-dicarboxylate (RS)-6

Diester (*RS*)-**1** (2.98 g, 10 mmol) was brominated as described by Mislow.[11] A mixture of the obtained crude dibromo diester (*RS*)-**2**, sodium azide (1.95 g, 30 mmol) and DMF (30 ml) was stirred at r.t. for 15 h. The mixture was partitioned between ethyl acetate and water and the organic layer was dried (Na_2SO_4) and concentrated. After dilution with dioxane (100 ml), triphenylphosphine (7.86 g, 30 mmol) was added portionwise. The mixture was stirred at r.t. for 6 h, water (0.5 ml, 31 mmol) was added and stirring was continued for 16 h. The solvent was evaporated in vacuo, the residue was mixed with chloroform (120 ml) and extracted with 2 M HCl (8×20 ml). The combined aqueous phases were washed with chloroform (5×15 ml) and evaporated in vacuo at a slightly elevated temperature. The dry residue was dissolved in boiling methanol (35 ml), filtered, and the hydrochloride of (*RS*)-**6** was precipitated with dry ether, m.p. 228–232°C (dec.). Overall yield 1.72 g (41%). ^{1}H NMR (200 MHz, D_2O) δ 8.10–7.65 m, 6H; 3.98 d and 3.70 d, 4H, J=14.6; 3.65 s, 6H. MS (FAB) m/z, %: 329 (100, M+1−2HCl). Anal. Calcd for $C_{18}H_{22}Cl_2N_2O_4 \cdot H_2O$: C, 51.56; H, 5.77; Cl, 16.91; N, 6.68. Found: C, 51.65; H, 5.49; Cl, 17.11; N, 6.67.

6.2. (S)-Dimethyl 6,6′-bis(aminomethyl)-1,1′-biphenyl-2,2′-dicarboxylate (S)-6

Diester[8] (*S*)-**1** ($[\alpha]_D$ +48.3 (c 0.5, methanol); 10.0 g, 33.5 mmol) was converted into the dihydrochloride of (*S*)-6 as described for the racemate except that crystallization of (*S*)-**6** was omitted. The product was a solid mass of $[\alpha]_D^{20}$ +101.2 (c 0.5, water) and had the same ^{1}H NMR spectrum as the racemate.

6.3. (RS)-5,11-Diaza-4,10-dioxo-4,5,6,10,11,12-hexahydrodibenzo[ef,kl]heptalene (RS)-1

(a) A solution of dihydrochloride of (*RS*)-**6** (100 mg, 0.25 mmol) in dry methanol (1 ml) was mixed with 1 M sodium methoxide in methanol (1 ml). After stirring at r.t. for 16 h, the mixture was diluted with ether (2 ml) and the remaining solid was collected, washed with water, dissolved in methanol and passed through a short column of silica gel. Yield 55 mg (87%), m.p. >360°C (methanol; sublimation above 300°C). The compound was not resolved on any accessible chiral column. ^{1}H NMR (200 MHz,

$(CD_3)_2SO$): δ 8.68 t, 2H, J=6.5; 7.45–7.80 m, 6H; 4.02 dd and 3.85 dd, 4H, J_1=13.1, J_2=6.5. MS (FAB): 265 (M+1). Anal. Calcd for $C_{16}H_{12}N_2O_4 \cdot 0.5CH_3OH$: C, 70.70; H, 5.03; N, 9.99. Found: C, 70.57; H, 4.76; N, 10.15.

(b) Crude diazido ester (*RS*)-**5** (0.92 g), prepared from crude dibromo ester (*RS*)-**3** (*vide supra*), was hydrogenated over 10% Pd/C (0.3 g) in methanol (50 ml) by introducing a gentle stream of hydrogen into the solution for 2 h. The catalyst was filtered off, the solvent evaporated and the crude amino ester (0.75 g) was dissolved in methanol (2 ml). After addition of 1 M methanolic sodium methoxide (2 ml) and standing at r.t. for 16 h, the deposited (*RS*)-**1** (0.20 g; 38%) from (*RS*)-**3** was collected and washed with methanol and ether.

(c) Dihydrochloride of (*RS*)-**6** (100 mg) was heated at 250°C for 15 min. After cooling, the reaction mixture was dissolved in methanol and filtered through a short column of silica gel. Evaporation of the solvent gave 60 mg (90%) of (*RS*)-**1**, pure according to the NMR spectrum.

*6.4. (S)-(+)-5,11-Diaza-4,10-dioxo-4,5,6,10,11,12-hexahydrodibenzo[ef,kl]-heptalene (S)-**1***

A solution of dihydrochloride of (*S*)-**6**, $[\alpha]_D^{20}$ +101.2 (100 mg, 0.25 mmol) in dry methanol (1 ml) was treated with 1 M methanolic sodium methoxide (1 ml) at 0°C for 5 days. The mixture was concentrated at low temperature and flash chromatographed on a silica gel column in ethyl acetate:ethanol:water (4:2:1) to give 57 mg (86%) of product (*S*)-**1**, $[\alpha]_D^{20}$ +471.0 (c 0.2, methanol). Attempted enantiopurification by crystallization failed since the racemate was evidently less soluble than the pure enantiomer. CD (50% aqueous methanol), λ, nm, ($\Delta\varepsilon$, 1 mol^{-1} cm^{-1}): 258 (+34.6), 237 (+7.0), 222 (+29.7). Rates of racemization in methanol: $k_{23}=5.18\times10^{-6}$ s^{-1} ($\Delta G^{\#}$=104.2 kJ/mol); $k_{50.5}=2.2\times10^{-4}$ s^{-1} ($\Delta G^{\#}$=104.1 kJ/mol). The ^{1}H NMR spectrum was identical with that of the racemic compound. When the cyclization reaction was performed at r.t. (16 h), the product had $[\alpha]_D^{20}$ +361.3.

*6.5. 2′,6′-Bis(hydroxymethyl)-1,1′-biphenyl-2,6-dicarboxylic acid **8***

A mixture of tetra aldehyde[12] **7** (5.32 g, 20 mmol) and 6 M aqueous NaOH (100 ml) was stirred at 20–30°C for 1 h. After cooling and filtration, the mixture was acidified with conc. HCl and the white precipitate was collected and crystallized from boiling water to give 4.13 g (68%) of the product, m.p. 210–214°C (decomp.) and remelting at 286–288°C (formation of the corresponding dilactone for which was reported[7] m.p. 284–287°C). ^{1}H NMR ($(CD_3)_2SO$) δ 12.7 br s, 2H; 7.87 d, 2H, J=7.6; 7.58 t, 1H, J=7.6; 7.25–7.40 m, 3H; 5.1 br s, 2H; 4.08 s, 4H.

*6.6. 2′,6′-Bis(bromomethyl)-1,1′-biphenyl-2,6-dicarboxylic acid **9***

Dihydroxy diacid **8** (4.10 g, 13.56 mmol) was refluxed with 46% aqueous HBr (40 ml) under stirring for 8 h. After cooling and dilution with water (50 ml), the precipitate was collected, washed with water and dried *in vacuo*. Yield 5.44 g (94%), m.p. 285–288°C (decomp.). ^{1}H NMR ($(CD_3)_2SO$) δ 8.13 d, 2H, J=7.6; 7.69 t, 1H, J=7.6; 7.28–7.48 m, 3H; 4.19 s, 4H.

*6.7. Dimethyl 2′,6′-bis(bromomethyl)-1,1′-biphenyl-2,6-dicarboxylate **10***

The crude dibromo diacid **9** (3.00 g, 7 mmol) was esterified with diazomethane in ether to give diester **10** (3.18 g, 99%), m.p. 119–119.5°C (aqueous methanol). ^{1}H NMR ($CDCl_3$) δ 8.22 d, 2H, J=7.6; 7.65 t, 1H, J=7.6; 7.32–7.50 m, 3H; 4.12 s, 4H; 3.60 s, 6H. MS (FAB): *m/z* (relative intensity) 459, 457, 455

(MH$^+$, 10, 20, 10), 377 (53), 375 (52), 251 (58), 237 (100), 221 (58), 207 (56), 179 (75), 177 (81), 165 (65), 93 (65), 91 (66), 73 (68), 57 (70). Anal. Calcd. for $C_{18}H_{16}Br_2O_4$: C, 47.40; H, 3.54; Br, 35.04. Found C, 47.68; H, 3.52; Br, 35.03.

6.8. Dimethyl 2′,6′-bis(azidomethyl)-1,1′-biphenyl-2,6-dicarboxylate ***11***

Dibromo diester **10** (3.18 g, 6.97 mmol) and sodium azide (1.4 g, 21.5 mmol) in DMF (50 ml) were stirred at 50°C for 3 h. Water (150 ml) was added and the azido ester was collected, washed with water and dried *in vacuo* at r.t. Yield 2.61 g (98%), m.p. 75–75.5°C. ^{1}H-NMR ($CDCl_3$) δ 8.13 d, 2H, J=7.6; 7.61 t, 1H, J=7.6; 7.36–7.52 m, 3H; 3.97 s, 4H; 3.61 s, 6H. MS (FAB) *m/z* (relative intensity): 381 (MH$^+$, 33), 355 (65), 293 (100), 234 (97), 220 (63), 206 (97), 192 (94), 165 (71), 93 (74), 59 (72).

*6.9. (*R,S*)-5,11-Diaza-4,12-dioxo-4,5,6,10,11,12-hexahydrodibenzo[ef,kl]heptalene (*RS*)-2*

Diazido ester **11** (1.24 g, 3.26 mmol) was hydrogenated over 10% Pd/C (60 mg) in methanol (50 ml) by bubbling the hydrogen through the stirred mixture. The originally suspended ester dissolved and after 3 h the reaction was finished. Removal of the catalyst and evaporation of the solvent gave the product (*RS*)-**12** as an oil which on standing at r.t. solidified upon spontaneous lactamization. Crystallization from 70% aqueous acetonitrile afforded 0.75g (87%) of pure dilactam (*RS*)-**2**, not melting up to 360°C. ^{1}H NMR ($(CD_3)_2SO$) δ 8.71 t, 2H, J=6.1; 7.91 d, 2H, J=7.6; 7.63 t, 1H, J=7.6; 7.34–7.58 m, 3H; 3.96 dd and 3.86 dd, 4H, J_1=14.5, J_2=6.1. MS (FAB) *m/z* (relative intensity): 266 (MH_2^+, 26), 265 (MH$^+$, 100), 215 (15), 201 (18), 181 (20), 110 (43), 91 (86), 75 (48), 73 (55), 57 (72). Anal. Calcd for $C_{16}H_{12}N_2O_2 \cdot H_2O$: C, 68.08; H, 5.00; N, 9.92. Found C, 68.13; H, 5.00; N, 9.63.

*6.10. (*R*)- and (*S*)-5,11-Diaza-4,12-dioxo-4,5,6,10,11,12-hexahydrodibenzo[ef,kl]heptalene (*R*)- and (*S*)-2*

The racemate (*RS*)-**2** (110 mg) was resolved by HPLC on a 60×3 cm triacetylcellulose column, eluent 96% ethanol, flow rate 4 ml/min, injections 25 mg in 5 ml of 60% aq. ethanol (dissolved in boiling solvent and injected warm). Further chromatography gave 30.2 mg of the (+)-antipode (eluted first), $[\alpha]_D^{20}$ +517.3 (c 0.2, methanol); CD (50% aq. methanol), λ, nm, (Δε, l mol^{-1} cm^{-1}): 260 (+38.8), 240 (+17.8), 226 (+28.3). The second eluted was the (−)-antipode (31.2 mg), $[\alpha]_D^{20}$ −511.2 (c 0.2, methanol). Rates of racemization in methanol: $k_{50.5}=6.51\times10^{-4}$ s^{-1} ($\Delta G^{\#}$=101.1 kJ/mol).

6.11. Single crystal X-ray diffraction analysis

(*RS*)-**1**·0.5MeOH, $C_{16}H_{12}N_2O_2 \cdot 0.5CH_3OH$, M=280.30, orthorhombic, space group *Pbcn* (No. 60), *a*=21.019(3), *b*=7.667(2), *c*=16.111(9), *V*=2596(2) Å^3, *F*(000)=1176, D_c=1.434 g/cm^3, *Z*=8. A colourless needle of dimensions 0.28×0.33×0.78 mm (grown from methanol) was measured on a CAD4 diffractometer at 293(2)K with MoK_α radiation, λ=0.71073 Å. From a total of 2836 reflections measured in the range *h*=0 to 24, *k*=0 to 9, *l*=−19 to 19, 2286 were independent (R_{int}=0.026) and 1720 of those were regarded as observed according to the $I>2\sigma(I)$ criterion. Absorption was neglected (μ=0.098 mm^{-1}). The structure was solved by direct methods (SHELXS86)[13] and refined by full-matrix least squares based on F^2 (SHELXL93).[14] The carbon-bonded hydrogens were fixed in calculated positions, amide hydrogens were refined isotropically and assigned the temperature parameters 1.2 of those of their bonding partners. The methanol molecule is disordered and was modelled as two 50:50 positions of oxygen and one of

carbon (located at a symmetry element); methanol hydrogens were not found. The refinement converged to R=0.0559, wR=0.1453, GOF=1.109 for 203 parameters, maximal residual electron density around the disordered methanol was −0.28e Å^{-3}. The atomic coordinates, bond lengths and angles were deposited by CSD. Full crystallographic data in the form of standard CIF files as produced by SHELX are available by e-mail from the author (J.P.).

(*RS*)-**2**·H_2O, $C_{16}H_{14}N_2O_3$, M=282.29, monoclinic, space group $P2_1/c$ (No. 14), a=8.5371(6), b=15.071(1), c=10.7831(9) Å, β=109.208(6)° V=1310.2(2) Å^3, F(000)=592, D_c=1.431 g/cm^3 for Z=4. Colourless parallelepiped, 0.31×0.27×0.35 mm (from hot 70% aqueous ethanol by slow cooling to r.t.). Total of 2519 reflections (h=−10 to 9, k=0 to 17, l=0 to 12), 2293 independent (R_{int}=0.011) and 1914 observed (μ=0.101 mm^{-1}). The O- and N-bonded hydrogen atoms were refined isotropically, the C-bonded hydrogens were fixed in calculated positions. Final values R=0.0315, wR=0.0795, GOF=1.044 for 207 parameters. The final difference map displayed no peaks of chemical significance. For other details see the previous structure.

Acknowledgements

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