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Racemic and Meso Crystal Structures of an Axial-Chiral Spirobi-(dinaphthoazepin)ium Salt: Emergence of an $S_4$-Symmetric Molecule

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Abstract: To date, only a few instances of $S_4$-symmetric organic molecules exist. In principle, spirobi-(dinaphthoazepin)ium cations can achieve this highly symmetric point group. Heating racemic 2,2′-bis(bromomethyl)-1,1′binaphthyl with aqueous ammonia afforded a mixture of rac- and meso-3,3′,5,5′-tetrahydro-4,4′-spirobi[dinaphtho[2,1-c;1′,2′-e]azepin]-4-ium bromide which was separated by fractional crystallisation. Both stereoisomers were characterised spectroscopically, and their crystal structures were determined and compared. The rac crystal structure differs significantly from the known enantiopure one. The meso molecules display a near-perfect $S_4$ symmetry. Upon treatment with KO$^\text{t}$Bu, both isomers undergo Stevens rearrangement.

Keywords: crystal structure; three-dimensional structure; chirality; axial chirality; racemate; meso; spiro compound; Stevens rearrangement

1. Introduction

Dinaphthoazepinium compounds (Figure 1) have found widespread application as chiral phase transfer catalysts [1,2]. Structural variations comprised introduction of various bulky substituents ($R^1$ in pos. 3 and 3′), preferably using semi-rigid aromatic groups, and the quarterisation of nitrogen ($R^2 =$(cyclo)alkyl or benzylic moieties, etc.). Of particular interest is the formation of N-spiro compounds where a dibenzo- with a dinaphthoazepine (C) or two dinaphthoazepines (D) are merged, resulting in a conformatively stable ammonium ion [3–8]. In cases A and B, a product with $C_2$ symmetry is formed. The same is true for D if connecting binaphthyls with the same chirality. The situation is less obvious in case C, where the conformation of the biphenyl moiety is controlled by the binaphthyl chirality. If combining identical homochiral units in case D ($R^1 = H$), a spiro compound with $D_2$ symmetry is obtained as confirmed by X-ray analysis; from binaphthyl halves with opposite chirality, an achiral species with $S_4$ symmetry may result.

In view of the intended application in PTC, only non-racemic material was synthesised so far, and to the best of our knowledge, racemic precursors such as rac-1 have never been used as intermediate in the synthesis of 2 (Figure 2).
2. Materials and Methods

2.1. General

Melting points were measured on a Reichelt Thermovar Kofler apparatus, uncorrected. NMR spectra were recorded on a Bruker AV III 400 spectrometre at 400.27 MHz (\(^{1}\text{H}\)) and 100.66 MHz (\(^{13}\text{C}\)), and a Bruker AV III 600 at 600.25 MHz (\(^{1}\text{H}\)) and 150.95 MHz (\(^{13}\text{C}\)), respectively (Bruker Biospin, Billerica, MA, USA); chemical shifts \(\delta\) are reported in ppm rel. to solvent signals (7.26 and 77.00 ppm for CHCl\(_{3}\)/CDCl\(_{3}\), and 5.32 and 53.5 ppm for CD\(_{2}\)Cl\(_{2}\), respectively). Coupling patterns are designated as s(inglett), d(oublett), t(riplett), m(ultiplet), p(seudo), and br(oad). \(^{13}\text{C}\{^{1}\text{H}\}\) NMR spectra are recorded in a J-modulated mode; signals are assigned as C, CH, CH\(_{2}\), and CH\(_{3}\). HRMS were recorded by an ESI FINNIGAN MAT 8230 mass spectrometre (Bruker Daltonics, Bremen, Germany). For HPLC determination of chiral products, an Agilent 1200 chromatograph equipped with a diode array detector and auto sampler was used (Agilent Technologies, Waldbronn, Germany).

Heptane and dichloromethane (DCM) were distilled prior to usage. Absolute THF was distilled from sodium benzophenone ketyl. All the other chemicals were analytical grade and used without further purification. Column chromatography was performed on an Isolera One system (Biotage Sweden AB, Uppsala, Sweden) with self-packed columns, SiO\(_{2}\), 40–63 \(\mu\)m. Racemic 2,2\(^{\prime}\)-bis(bromomethyl)-1,1\(^{\prime}\)-binaphthalene I, (\(R\))\(_{ax}\)-I, and (\(S\))\(_{ax}\)-4,5-dihydro-3H-dinaphth[2,1-c:1',2'-e]azepine (\(S\))\(_{ax}\)-3 were prepared according to literature [3,9,10].
2.2. Synthesis and Crystallisation

2.2.1. Synthesis of meso- and rac-3,3′,5,5′-Tetrahydro-4,4′-spirob[azepino[2,1-c:1′,2′-e]azepin]-4-ium Bromide, meso-2, and rac-2

rac-2,2′-Bis(bromomethyl)-1,1′-binaphthalene rac-1 (3.38 g, 7.68 mmol) was placed in a steel autoclave equipped with glass insert and stirrer. Toluene (40 mL) and aqueous ammonia (25%, 20 mL) was added, and the mixture was vigorously stirred for 24 h at 80–90 °C. After cooling to r.t., the slurry was transferred to a flask, and excess ammonia and toluene was removed under vacuum. The crystalline precipitate was separated, washed carefully with water and Et2O, and dried to give 2.489 g (99%) of azepinium bromide 2 as mixture of meso-2 and rac-2 slightly varying in composition (45:55) separable by fractional crystallisation.

In a typical run, 1.004 g of the mixture was dissolved in THF (23 mL)/MeOH (15 mL) with gentle warming. After reducing the volume to 15 mL by slow evaporation, the crystalline material (490 mg) was separated, containing 84% of meso-2 and 16% of rac-2. A second crystallisation (20 mL THF and 10 mL MeOH) afforded 280 mg (28%) of pure meso-2. The mother liquor of the first crystallisation was evaporated and the residue dissolved in MeOH (4 mL). After removal of some crystalline material of low purity (148 mg), the mother liquor was evaporated to give 376 mg (37%) pure rac-2; mixed fractions (348 mg) could be combined and recycled.

HPLC analysis: Chiralcel-ODH (4.6 × 250 mm) in MeOH (12.5%), EtOH (12.5%), heptane (74.7%), TFA (0.3%), 0.5 mLmin⁻¹, tR[(R,S)ax-2] = 9.3 min, tR[(R,R)ax-2] = 11.0 min, tR[(S,S)ax-2] = 14.6 min (Supplementary Materials, Figure S1).

meso-2: m.p.: 315–325 °C (decomposition). 1H NMR (CD2Cl2) δ: 8.15 (br.d, J = 8.4 Hz, 4H); 8.10 (dm, J = 8.2 Hz, 4H); 7.69 (d, J = 8.2 Hz, 4H); 7.66 (ddd, J = 8.1, 6.8, 1.2 Hz, 4H); 7.54 (dm, J = 6.8 Hz, 4H); 7.43 (ddd, J = 8.2, 6.9, 1.4 Hz, 4H); 4.47 (d, J = 12.8 Hz, 4H), 4.43 (d, J = 12.8 Hz, 4H) ppm.

13C NMR (CD2Cl2) δ: 137.23 (C); 134.89 (C); 136.44 (C); 130.77 (CH); 128.83 (CH); 127.84 (CH); 127.64 (CH); 127.41 (CH); 127.07 (CH); 126.23 (C); 65.17 (CH2) ppm.

HRMS (ESI): calculated for C44H32N [M-Br]⁺: 574.2535, found 574.2548. rac-2: m.p.: 330–345 °C (decomposition).

Spectroscopic data agree with literature for the non-racemic compound [3,10]. Applying the same procedure to (R,R)-meso-2 afforded 94% of (R,R)-meso-2 as a pale yellow powder. 1H NMR showed >98% purity.

2.2.2. Synthesis of meso-3,3′,5,5′-Tetrahydro-4,4′-spirob[azepino[2,1-c:1′,2′-e]azepin]-4-ium Bromide, (R,S)ax-2

A mixture of (S)ax-4,5-dihydro-3H-dinaphth[2,1-c:1′,2′-e]-azepine (S)ax-3 (295 mg, 1mmol), 2,2′-bis(bromomethyl)-1,1′-binaphthalene (R)ax-1 (440 mg, 1mmol), and K2CO3 (2 mmol, 280 mg) in 20 mL of acetonitrile was stirred at 80 °C for 24 h under argon. Water (50 mL) and DCM (100 mL) were added and the aqueous layer was extracted once with DCM (100 mL). The combined organic phases were dried with MgSO4 and evaporated to give 645 mg (99%) of (R,S)ax-2 as a pale yellow powder. 1H NMR showed >98% purity.

2.2.3. Synthesis of 11,13,26,26a-Tetrahydrodinaphtho[2′,1′:3,4;1″,2″′-5,6]azepino[1,2-a]dinaphtho[2,1-d:1′,2′-f]azocine; (S)C(R,R)ax-4 (racemate)

To a suspension of rac-3,3′,5,5′-tetrahydro-4,4′-spirob[dinaphtho[2,1-c:1′,2′-e]azepin]-4-ium bromide rac-2 (0.1 mmol) in DCM (1 mL) KOBu (22.5 mg, 0.2 mmol, 2 equivalents) was added. After stirring at r.t. overnight, the mixture was partitioned between water (5 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (3 × 3 mL); the combined organic layers were washed with water (5 mL), dried (Na2SO4), and the solvent was evaporated. The residue was purified by chromatography (SiO2, heptane/EtOAc (0–15%)) to afford 51 mg (85%) of 4 as a crystalline powder. m.p.: 235 °C (slow decomposition above 200 °C).
\[ ^1H \text{NMR} (\text{CDCl}_3) \delta: \ 8.01 \ (d, J = 8.5 \ \text{Hz}, 1H); 7.95 \ (d, J = 7.0 \ \text{Hz}, 1H); 7.93 \ (d, J = 7.5 \ \text{Hz}, 1H); 7.90 \ (\text{br.d}, J = 8.5 \ \text{Hz}, 2H); 7.84 \ (d, J = 8.2 \ \text{Hz}, 1H); 7.77 \ (d, J = 8.5 \ \text{Hz}, 1H); 7.76 \ (d, J = 8.0 \ \text{Hz}, 1H); 7.68 \ (d, J = 8.5 \ \text{Hz}, 1H); 7.67 \ (d, J = 8.5 \ \text{Hz}, 1H); 7.61 \ (d, J = 8.7 \ \text{Hz}, 1H); 7.41–7.50 \ (\text{m}, 4H); 7.40 \ (d, J = 8.1 \ \text{Hz}, 1H); 7.36 \ (m, 1H); 7.34 \ (m, 1H); 7.23–7.26 \ (m, 3H); 7.15–7.18 \ (m, 2H); 7.15 \ (d, J = 8.5 \ \text{Hz}, 1H); 4.06 \ (d, J = 13.1 \ \text{Hz}, 1H); 3.92 \ (d, J = 14.2 \ \text{Hz}, 1H); 3.85 \ (d, J = 14.2 \ \text{Hz}, 1H); 3.59 \ (m, 1H); 3.28 \ (d, J = 13.1 \ \text{Hz}, 1H); 3.11 \ (m, 2H) \text{ppm.} \]

\[ ^{13}C \text{NMR} (\text{CDCl}_3) \delta: \ 140.05 \ (C); 138.96 \ (C); 138.16 \ (C); 135.26 \ (C); 133.88 \ (C); 133.22 \ (C); 133.05 \ (2C); 132.95 \ (C); 132.71 \ (C); 132.52 \ (C); 132.30 \ (C); 132.15 \ (C); 131.98 \ (C); 131.28 \ (C); 130.78 \ (C); 129.13 \ (CH); 128.96 \ (CH); 128.78 \ (CH); 128.73 \ (CH); 128.70 \ (CH); 128.38 \ (CH); 128.32 \ (CH); 128.25 \ (CH); 128.05 \ (CH); 127.80 \ (CH); 127.70 \ (3CH); 127.40 \ (CH); 126.41 \ (CH); 125.90 \ (CH); 125.87 \ (CH); 125.82 \ (CH); 125.69 \ (CH); 125.47 \ (CH); 125.33 \ (CH); 125.30 \ (CH); 125.02 \ (CH); 123.81 \ (CH); 63.35 \ (CH); 53.11 \ (CH); 127.56 \ (CH); 127.44 \ (CH); 127.00 \ (CH); 126.15 \ (CH); 125.94 \ (CH); 125.76 \ (CH); 125.70 \ (CH); 125.60 \ (CH); 125.44 \ (CH); 125.38 \ (CH); 125.34 \ (CH); 125.12 \ (CH); 60.16 \ (CH2); 54.31 \ (CH); 53.11 \ (CH2); 38.12 \ (CH2) \text{ppm.} \]

5. \[ ^1H \text{NMR} (400 \ \text{MHz}, \text{CDCl}_3) \delta: \ 6.82–8.05 \ (\text{m}, 24H); 4.02 \ (m, 1H); 4.00 \ (d, J = 10.4 \ \text{Hz}, 1H); 3.99 \ (d, J = 13.9 \ \text{Hz}, 1H); 3.42 \ (dd, J = 14.7, 5.5 \ \text{Hz}, 1H); 3.30 \ (d, J = 13.9 \ \text{Hz}, 1H); 3.10 \ (dd, J = 14.7, 3.2 \ \text{Hz}, 1H); 2.99 \ (d, J = 10.3 \ \text{Hz}, 1H) \text{ppm.} \]

6. \[ ^1H \text{NMR} (400 \ \text{MHz}, \text{CDCl}_3) \delta: \ 6.73–5.15 \ (\text{m}, 24H); 4.37 \ (d, J = 14.2 \ \text{Hz}, 1H); 4.24 \ (d, J = 14.2 \ \text{Hz}, 1H); 4.23 \ (d, J = 8.3 \ \text{Hz}, 1H); 4.06 \ (d, J = 14.2 \ \text{Hz}, 1H); 3.77 \ (d, J = 14.2 \ \text{Hz}, 1H); 2.30 \ (d, J = 13.6 \ \text{Hz}, 1H); 1.69 \ (dd, J = 13.6, 8.3 \ \text{Hz}, 1H) \text{ppm.} \]

7. \[ ^1H \text{NMR} (400 \ \text{MHz}, \text{CDCl}_3) \delta: \ 8.00 \ (d, J = 8.3 \ \text{Hz}, 1H); 7.97 \ (\text{dm}, J = 8.2 \ \text{Hz}, 1H); 7.85–7.92 \ (m, 7H); 7.69 \ (d, J = 8.6 \ \text{Hz}, 1H); 7.66 \ (d, J = 8.6 \ \text{Hz}, 1H); 7.52 \ (d, J = 8.0 \ \text{Hz}, 1H); 7.48 \ (\text{ddd}, J = 7.9, 6.7, 1.1 \ \text{Hz}, 1H); 7.42 \ (d, J = 8.3 \ \text{Hz}, 2H); 7.38–7.43 \ (m, 3H); 7.36 \ (\text{dm}, J = 8.7 \ \text{Hz}, 2H); 7.28 \ (\text{ddd}, J = 8.4, 6.9, 1.4 \ \text{Hz}, 1H); 7.24 \ (m, 1H); 7.20 \ (\text{ddd}, J = 8.2, 6.8, 1.4 \ \text{Hz}, 2H); 3.86 \ (dd, J = 3.6, 2.4 \ \text{Hz}, 1H); 3.75 \ (d, J = 12.2 \ \text{Hz}, 2H); 3.32 \ (dd, J = 15.0, 2.3 \ \text{Hz}, 1H); 3.04 \ (dd, J = 15.9, 3.7 \ \text{Hz}, 1H); 3.01 \ (d, J = 12.3 \ \text{Hz}, 2H) \text{ppm.} \]

\[ ^{13}C \text{NMR} (151 \ \text{MHz}, \text{CDCl}_3) \delta: \ 138.57 \ (C); 135.08 \ (C); 134.91 \ (2C); 134.11 \ (2C); 133.90 \ (C); 133.37 \ (C); 132.86 \ (2C); 132.24 \ (C); 131.27 \ (C); 131.22 \ (2C); 130.75 \ (C); 130.51 \ (C); 128.28 \ (CH); 128.16 \ (CH); 128.13 \ (2CH); 128.09 \ (2CH); 127.93 \ (4CH); 127.89 \ (CH); 127.53 \ (CH); 127.49 \ (CH); 127.39 \ (2CH); 126.72 \ (CH); 125.55 \ (2CH); 125.38 \ (CH); 125.23 \ (2CH); 124.90 \ (CH); 124.76 \ (CH); 124.49 \ (CH); 60.69 \ (CH); 52.52 \ (2CH_2); 35.82 \ (CH_2) \text{ppm.} \]

HRMS (ESI): calculated for C_{46}H_{32}N [M+H^+]: 574.2535, found 574.2529.
2.2.5. N-Methylation of 4

To a solution of 11,13,26,26a-Tetrahydrodinaphtho[2′,1′:3,4;1″,2″:5,6], azepino[1,2-a]dinaphtho[2,1-d:1′,2′-f]azocine 4 (26 mg, 0.05 mmol) in acetonitrile (0.5 mL)/DCM (1.5 mL), excess of CH$_3$I was added and the reaction was stirred until TLC indicated absence of substrate. Evaporation of solvents left a viscous oil of pure N-methyl ammonium iodide of 4 in quantitative yield.

$^1$H NMR (CDCl$_3$) $\delta$: 8.85 (d, $J = 8.6$ Hz, 1H); 8.16 (d, $J = 8.7$ Hz, 1H); 8.13 (d, $J = 8.7$ Hz); 8.04 (d, $J = 8.4$ Hz, 1H); 8.02 (d, $J = 9.0$ Hz, 1H); 7.98 (d, $J = 8.4$ Hz, 1H); 7.96 (d, $J = 8.4$ Hz, 1H); 7.94 (d, $J = 8.4$ Hz, 1H); 7.73 (d, $J = 8.1$ Hz, 1H); 7.66 (d, $J = 8.4$ Hz, 1H); 7.62 (ps.t, $J = 8.5$ Hz, 1H); 7.52–7.60 (m, 4H); 7.42 (m, 2H); 7.22 (ps.t, $J = 7.7$ Hz, 1H); 7.17 (ps.t, $J = 7.9$ Hz, 1H); 7.00 (d, $J = 8.4$ Hz, 2H); 6.81 (d, $J = 8.4$ Hz, 1H); 6.56 (d, $J = 13.4$ Hz, 1H); 6.23 (d, $J = 13.0$ Hz, 1H); 4.21 (d, $J = 8.3$ Hz, 1H); 4.09 (d, $J = 12.8$ Hz, 1H); 3.78 (d, $J = 13.4$ Hz, 1H); 3.67 (d, $J = 15.7$ Hz, 1H); 3.43 (dd, $J = 15.8$ Hz, 1H); 3.01 (s, 3H) ppm.

$^{13}$C NMR (CDCl$_3$) $\delta$: 137.72 (C); 137.39 (C); 136.53 (C); 135.94 (C); 134.40 (C); 133.96 (C); 133.94 (C); 132.31 (C); 132.29 (C); 132.15 (C); 132.07 (CH); 131.61 (C); 130.89 (CH); 130.87 (C); 130.84 (CH); 130.82 (C); 130.58 (C); 130.45 (CH); 129.42 (CH); 128.82 (CH); 128.52 (CH); 128.28 (CH); 128.03 (CH); 128.01 (CH); 127.89 (CH); 127.85 (CH); 127.65 (CH); 127.48 (CH); 127.35 (CH); 127.20 (CH); 127.15 (CH); 127.10 (CH); 127.05 (2CH); 126.81 (CH); 126.47 (C); 126.24 (CH); 125.74 (CH); 123.45 (CH); 74.64 (CH); 70.47 (CH$_2$); 65.33 (CH$_2$); 42.72 (CH$_3$); 32.44 (CH$_2$) ppm.

HRMS (ESI): calculated for C$_{45}$H$_{34}$N [M-I$^+$]: 588.2686, found 588.2677.

2.3. X-ray Diffractometry

The X-ray intensity data were measured on Bruker D8 Venture diffractometer equipped with multilayer monochromator, Mo K$_\alpha$ INCOATEC micro-focus sealed tube, and Oxford cooling system. The structures were solved by direct methods (rac-2,4) or charge flipping (meso-2). Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted at calculated positions and refined with riding model. C-H bond lengths in the aromatic and olefin bond systems were constrained at 0.950 Å, aliphatic CH$_2$ groups at 0.990 Å, and aliphatic CH$_3$ groups at 0.980 Å. The default values of SHELXL [11] were used for the riding-atom model. Fixed U$_{iso}$ values of 1.2 times were used for all C(H) and C(H,H) groups, and fixed U$_{iso}$ values of 1.5 times were used for all C(H,H,H) and O(H) groups.

The following software was used: Bruker SAINT software package [12] using a narrow-frame algorithm for frame integration; SADABS [13] for absorption correction; OLEX2 [14] for structure solution, refinement, molecular diagrams, and graphical user-interface; Shelyx [15] for refinement and graphical user-interface; SHELXS-2015 [11,16] for structure solution; SHELXL-2015 [11,17,18] for refinement; and Platon [19] for symmetry check. Crystal structure data is summarized in Table 1. For additional experimental parameters, see Table S1 in the Supplementary Materials.
Table 1. Crystal structure data of rac-2, meso-2 and 4.

|                     | Rac-2     | Meso-2    | 4        |
|---------------------|-----------|-----------|----------|
| M (g/mol)           | 1012.72   | 718.70    | 631.77   |
| Space group         | P-1       | C2/c      | P-1      |
| a (Å)               | 15.9737 (13) | 30.408 (2) | 11.5087 (4) |
| b (Å)               | 17.9202 (13) | 14.8246 (12) | 11.5335 (4) |
| c (Å)               | 18.7489 (19) | 16.0429 (11) | 13.5262 (5) |
| α (°)               | 117.544 (2) | 90        | 75.6052 (14) |
| β (°)               | 93.715 (4) | 103.653 (2) | 76.2673 (14) |
| γ (°)               | 108.646 (2) | 90        | 77.4586 (15) |
| V (Å³)              | 4362.0 (7) | 7027.6 (9) | 1665.30 (10) |
| Z                   | 4         | 8         | 2        |
| Rint                | 0.073     | 0.064     | 0.036    |
| R1 (I > 2σ(I))      | 0.057     | 0.055     | 0.044    |
| wR2 (all data)      | 0.191     | 0.151     | 0.119    |

3. Results and Discussion

3.1. Preparation of the Spiro Compounds

The unsubstituted parent compound was conveniently obtained by heating enantiomerically pure 2,2′-bis(bromomethyl)-1,1′-binaphthyl (S)ax-1 in toluene with aqueous ammonia at 80 °C for 24 h in an autoclave. After removal of solvent and thoroughly washing of the white crystalline precipitate with water (S,S)ax-2 was obtained in 94% yield. To the best of our knowledge, this simple “ammonia-route” was so far only used in a few cases [20,21]. Applying the same procedure to rac-1 afforded a mixture of diastereomers as expected. 1H-NMR showed the presence of rac-2/meso-2 in a ratio of 55:45.

A more pronounced preference for the formation of either diastereomer by varying reaction conditions failed. Acetone was not suitable because of self-condensation, even under mild reaction conditions. More appropriate seemed acetonitrile, but the reaction was slower, and up to 27% of dinaphthoazepine 3 was detected (NMR). DMF yielded a complex mixture. Additionally, the addition of phase transfer catalysts or Et3N did not alter the diastereomeric composition. Finally, temperatures between 80 and 100 °C, with efficient stirring in a two-phase system aqueous ammonia (25% v/v)/toluene were found to give the best results with the preferred formation of the rac-isomer. A preparative separation by chromatography was unsuccessful, but fractional crystallisation from THF/MeOH worked well. The crystalline material consisted largely of less-soluble meso-2 (84%), while rac-2 was enriched in the mother liquor (>90%). A second crystallisation afforded diastereomerically pure meso- and rac-2 in 28% and 37% yield, respectively (Supplementary Materials, Figures S2–S7). The combined mother liquors from the second crystallisation could be recycled.

Alternatively, meso-2 was obtained from (S)ax-1 and (R)ax-3 in quantitative yield.

3.2. Comparison of Solid-State Structures of meso-2 and rac-2 (Racemic and Enantiomeric)

Ready crystallisation of both diastereomers allowed the determination of the solid-state structure. Rac-2 with D2 symmetry crystallised in a non-chiral space group (P-1, Figure 3) differently from (S,S)ax-2 (I 212 1 21; [3]), while meso-2 revealed a nearly perfect S4 symmetry in the solid state (Figure 4), a point group rarely found in organic molecules [22–28]).
A more detailed inspection of structures showed significant deviations from ideal geometry, clearly visible when comparing the two azepinium units in each structure with different binaphthyl torsion angles (Table 2, Figure 5). Contrary to expectations, the structural peculiarities of diastereomers are less clearly evident. We find larger differences between the X-ray structures of rac-2 and enantiopure 2 (ref. [3]) than between rac-2 and meso-2. These differences obviously arise from packing effects.
Figure 4. Displacement ellipsoid plot (top) and chemical structure (bottom) of meso-2. The molecular structure is plotted twice to fully present each binaphthyl system. While the plot features two bromide counterions, their occupancy is 1/2; hence, the proper count of one counter atom is preserved.

Table 2. Crystal structure parameters of meso- and rac-2 (the structure of the mirror image \((S,S)_{ax}\)-2 was determined; CCDC code: GACVEM [3]) as well as \((R,R)_{ax}\)-2 and selected torsion angles, bond angles, and distances.

|                        | \((R,S)_{ax}\)-2 (meso) | \((R,R)_{ax}\)-2 [3] | \((R,R)_{ax}/(S,S)_{ax}\)-2 (rac) |
|------------------------|-------------------------|-----------------------|----------------------------------|
| Torsion angle C2-C11-C22-C13 [°] | 51.7(4)                | 50.7                  | 50.6(5)                          |
| Torsion angle C24-C33-C44-C35 [°] | 48.9(4)                | 55.5                  | 49.0(5)                          |
| Bond angle C1-N1-C12 [°]            | 109.8(2)               | 111.3                 | 110.9(3)                         |
| Bond angle C23-N1-C34 [°]            | 109.4(2)               | 109.9                 | 110.6(3)                         |
| Bond angle C1-N1-C34 [°]            | 109.5(2)               | 108.9                 | 112.1(3)                         |
| Bond angle C12-N1-C23 [°]           | 109.0(2)               | 108.9                 | 112.2(3)                         |
| Bond angle C2-C1-N1 [°]              | 112.0(3)               | 110.4                 | 113.8(3)                         |
| Bond angle C13-C12-N1 [°]            | 112.1(3)               | 110.4                 | 112.6(3)                         |
| Bond angle C24-C23-N1 [°]           | 111.7(3)               | 110.9                 | 113.5(3)                         |
| Bond angle C35-C34-N1 [°]            | 111.6(3)               | 110.9                 | 112.9(3)                         |
| Distance C1-N1 [Å]                  | 1.536(4)               | 1.522                  | 1.525(3)                         |
| Distance C12-N1 [Å]                 | 1.534(5)               | 1.522                  | 1.531(4)                         |
| Distance C23-N1 [Å]                 | 1.531(4)               | 1.540                  | 1.526(5)                         |
| Distance C34-N1 [Å]                 | 1.527(4)               | 1.540                  | 1.521(5)                         |
3.3. Attempted Separation of Enantiomers of 2

Chromatographic separation on an analytical scale allowed the simultaneous determination of enantio- and diastereomeric composition of the crude mixture of spiro-ammonium bromides using a Chiralcel-ODH column, but separation factors were too small to run separations on a preparative scale ($\alpha = 1.7$). Fractionated crystallisation experiments with chiral counter anions remained unsuccessful.

3.4. Stevens Rearrangement of 2

Having synthesised compounds rac-2 and meso-2 of relatively high symmetry, we were interested in possible subsequent syntheses. The high symmetry of the molecules and thus the chemical equivalency of the reactive sites prospects a limited number of possible isomeric products. The reactivity of dibenzo- and dinaphthoazepinium compounds was investigated in the past (Figure 6). With good nucleophiles, ring opening was observed [29], while treatment with strong bases (KO\textsubscript{t}Bu, PhLi) resulted in a Stevens rearrangement with ring contraction [30]. Merely, for tetrabenzoazepinium bromide, ring enlargement took place [31]. Additionally, non-racemic products were formed in the presence of chiral counter anions [32–34].

With tetranaphtho analogues 2, a similar behaviour was assumed, but as a consequence of rigidity of the structure, high regio- and stereocontrol of the rearrangement step was expected. Both meso- and rac-2 in THF were stirred with two equivalents of KO\textsubscript{t}Bu at r.t. overnight. NMR of the crude mixture revealed three (main) products derived from meso-2 but only one from rac-2 (Figure 7). All of these products are of the lowest molecular symmetry (C\textsubscript{1}).
Figure 6. Stevens rearrangement of benzo and naphtho-annelated azepinium compounds. a: PhLi, Et₂O, [30] b: phosphazene base (X⁻ = Bis(tetrachlorobenzenediolato)mono([1,1′]binaphthalenyl-2,2′-diolato)phosphate(V) anion) [32–34]) c: KO²Bu, THF, [30] d: Ag₂O/MeOH, 180–190 °C (Br⁻; [31]), phosphazene base (X⁻ = Bis(tetrachlorobenzenediolato)mono([1,1′]binaphthalenyl-2,2′-diolato)phosphate(V) anion) [32–34]).

Figure 7. Stevens Rearrangement of meso- and rac-2. Conditions: THF or DCM, KO²Bu (2 equivalent) r.t., 10 h. Relative configuration of products: (S)C(R,R)ax-4, (R)C(R,S)ax-5, (S)C(R,S)ax-6, (S)C(S,S)ax-7.

After chromatographic purification, the rearranged product from rac-2 crystallised from DCM/acetone thus confirmed structure 4 for the tertiary amine with relative (S)C(R,R)ax configuration (Figure 8). Under optimised conditions (DCM, two equivalents of KO²Bu at r.t. overnight), 4 was isolated in 85% yield (Supplementary Materials, Figures S8 and S9). Rearranged products from meso-2 formed under similar conditions could only be partly separated. The ring contracted product 7 was isolated in 16% yield, while two iso-
mers 5 and 6 (70:30) were obtained in 64% yield as a mixture (Supplementary Materials, Figures S10–S13).

Further variations of conditions (n-BuLi, CH₃ONa, NaH, DBU, equivalents of base, temperature, reaction time) afforded slower conversion or decomposition. In the case of meso-2, the selectivity could not be improved. Methylation of 4 yielded the ammonium salt quantitatively (Supplementary Materials, Figures S14 and S15). Subsequent treatment with KOᵗBu/THF at r.t. did not give any conversion. Applying more stringent conditions (n-BuLi in THF at r.t.) resulted in an inseparable mixture of products.

3.5. Intermolecular Structural Features

The crystal packing of the three crystal structures recorded is shown in Figure 9. Both rac-2 (Z = 4) and 4 (Z = 2) are of P-1 symmetry and organised into sheets parallel to (110). The packing of meso-2 (Z = 8) is more complex due to its higher C 2/c symmetry.
From those three crystal structures, only the crystal packing of rac-2 exhibits \( \pi-\pi \) interactions (Figure 10). In each case, the naphthyl planes of two opposite enantiomers overlap partially (Table S2 in the SI). Electrostatic interactions \( \text{Cl}_3\text{CH—Br} \) reminiscent of hydrogen bridges were found between the counter ion and the co-crystallised solvents (Table S3 in the SI).

Cosolvent–anion hydrogen bridges were also found in the crystal structure of meso-2 between MeOH and \( \text{Br}^- \) (Table S3 in the SI). Additional close contacts were found between the positively polarised \( \text{CH}_2 \) groups adjacent to the quaternary nitrogen in meso-2 and both the \( \text{Br}^- \) counter ion (\( d(\text{CH}_2—\text{Br}) = 2.764 \text{ Å}, 2.792 \text{ Å} \)) and the oxygen of MeOH (\( d(\text{CH}_2—\text{O}) = 2.425 \text{ Å}, 2.498 \text{ Å} \)) (Figure 11).
4. Conclusions

The spiro-compound 3,3′,5,5′-Tetrahydro-4,4′-spirobi[2H-naphtho[2,1-c:1′,2′-e]azepin]-4-ium bromide 2 was synthesised from a racemic precursor and separated into two diastereomers by fractional crystallisation: (1) the racemic crystals of (R,R)_{ax}/(S,S)_{ax}-2 and (2) the meso crystals of (R,S)_{ax}-2. While the former is a low-symmetry crystal structure (P-1) analogue of a known enantiopure crystal structure (I 2 1), the latter possesses a near-perfect S₄ improper rotation axis and belongs to point group S₄. This type of molecular symmetry is rare in organic chemistry and may be of interest in engineering molecules of high symmetry.

Of these crystal structures, only rac-2 exhibits π-π interactions. In both crystal structures, the co-crystallised solvents (MeOH and CHCl₃) interact with the Br⁻ counterions.

Both diastereomers undergo Stevens rearrangement when treated with t-BuOK. While meso-2 produced a mixture difficult to separate, the rearrangement of rac-2 occurred diastereoselectively and yielded the ring-expansion product (S)_{C}(R,R)_{ax}/(R)_{C}(S,S)_{ax}-4.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/sym13081365/s1, Figure S1: HPLC Separation of Stereoisomers of 2*, Figure S2: (R,S)_{ax}-2 (1H NMR in CDCl₃), Figure S3: (R,S)_{ax}-2 (1H NMR in CD₂Cl₂), Figure S4: (R,S)_{ax}-2 (13C NMR in CD₂Cl₂), Figure S5: (R,R)_{ax}/(S,S)_{ax}-2 (1H NMR in CDCl₃), Figure S6: (R,R)_{ax}/(S,S)_{ax}-2 (1H NMR in CD₂Cl₂), Figure S7: (R,R)_{ax}/(S,S)_{ax}-2 (13C NMR in CD₂Cl₂), Figure S8: (R,R)_{ax}/(S,S)_{ax}-4 (1H NMR in CDCl₃), Figure S9: (R,R)_{ax}/(S,S)_{ax}-4 (13C NMR in CDCl₃), Figure S10: mixture of 5 and 6 (70:30) (1H NMR in CDCl₃), Figure S11: mixture of 5 and 6 (70:30) (1H NMR in CDCl₃), Figure S12: 7 (1H NMR in CDCl₃), Figure S13: 7 (13C NMR in CDCl₃), Figure S14: N-Methyl ammonium iodide of 4 (1H NMR in CDCl₃), Figure S15: N-Methyl ammonium iodide of 4 (13C NMR in CDCl₃), Table S1: Experimental X-ray parameters and CCDC-Codes, Table S2: Short C-C contacts in rac-2, Table S3: Hydrogen bridges.

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