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Spontaneous generation of chirality and chiroptical spectra of *N*-nitroso-2,4-diaryl-3-azabicyclo[3.3.1]nonanes

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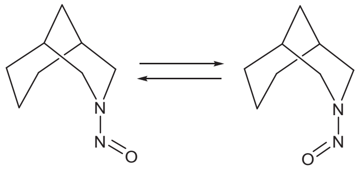
ABSTRACT

The crystal structures of several bicyclic *N*-nitrosamines indicate that they crystallize in the chiral (Sohncke) space group $P2_12_12_1$ as conglomerates. This allows the resolution of these compounds by manual picking of the enantiomorphous crystals. The optical activity of the single crystals was confirmed by their CD spectra taken in KBr disks. The absolute configurations of the title nitrosamines were assigned by crystallographic measurements and by a comparison of their CD spectra with those of a reference compound resolved by classical methods. The observed Cotton effect signs, corresponding to the n–π^* transition, were correlated with the helicity of the inherently chiral nitrosamine chromophore.

1. Introduction

N-Nitrosamines have been extensively investigated over the last three decades because of their strong carcinogenic and mutagenic properties.[1] They have also found synthetic applications as intermediates for the preparation of various *N*,*N*-bonded functionalities.[2] The restricted rotation about the N–N bond brought about by the polar resonance structure $>N^+{=}N{-}O^-$ leads to many unusual stereochemical features in these compounds. A weak long-wavelength absorption makes the *N*-nitrosamino chromophore an attractive model for spectroscopic studies.[2a,3] Their chiroptical properties have been the subject of many investigations in the last few years.[4]

The rigid 3-azabicyclo[3.3.1]nonane system upon N-substitution with a nitroso group loses its symmetry and becomes chiral. The conversion between the two enantiomers occurs by the rotation of the nitroso group (Scheme 1).



I *ent*-**I**

Scheme 1.

The title *N*-nitrosamines **1b–3b** owe their chirality solely to the restricted rotation about the N–N bond. In contrast, compounds **4a,b** and **6a,b** are chiral due to the desymmetrization of the bicyclic skeleton by methyl substitution at C-1. Our X-ray crystallographic studies and a literature survey revealed that the *N*-nitrosamines **1b–4b** crystallize in the chiral space group $P2_12_12_1$.[5,6] Usually this means that the racemic mixture forms a conglomerate; that is, a mechanical mixture of homochiral crystals wherein each single crystal is comprised of only one enantiomer.[7] Thus, the spontaneous generation of chirality occurs during the crystallization. This is a relatively rare and unpredictable phenomenon that deserves considerable attention due to it being one of the simplest and least expensive methods for the preparation of enantiomerically pure compounds. It may also have

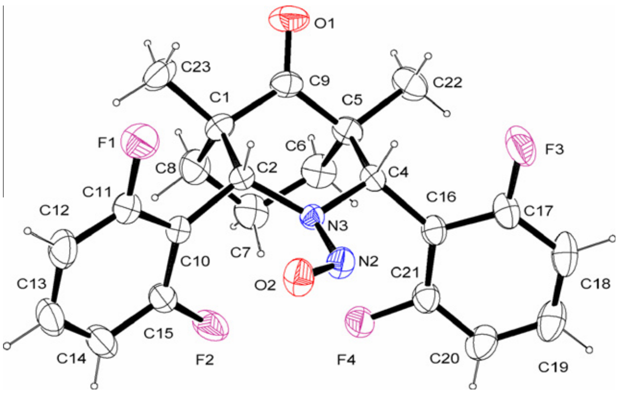


Figure 1. Molecular structure of *E*-**1b.** Displacement ellipsoids are drawn at the 30% probability level.

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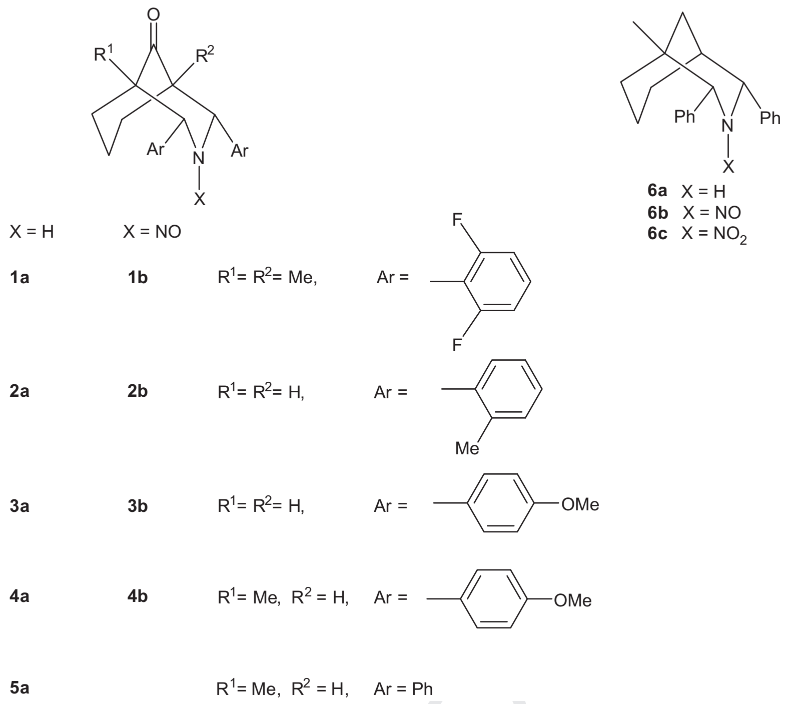
important implications for the prebiotic origin of chirality[8] or so-called ‘absolute’ asymmetric synthesis.[9]



Herein, we report the solid state CD spectra taken in KBr disks and correlate the observed Cotton effect signs with molecular chirality. In addition, we have resolved the chiral amine **6a** into its enantiomers and converted them into nitrosamines **6b**. This allowed us to study their solid state and solution CD spectra in relation to those of **1b–4b**. Due to the close relationship between the nitrosamine and nitramine chromophores,[10] nitrosamine **6b** was oxidized into *N*-nitramine **6c** whose chiroptical spectra were examined in order to gain further insight into the nature of the optical activity of the title compounds.

2. Results and discussion

2,4-Diaryl-3-azabicyclo[3.3.1]nonan-9-ones **1a**–**5a** were prepared by a Mannich condensation of substituted benzaldehydes with the appropriate cyclohexanones and ammonium acetate according to the literature.[5,11] Amine **6a** was obtained by a Wolff-Kishner reduction of ketone **5a**,[5] and then resolved into its enantiomers by crystallization of the diastereomeric salts with (*S*)-(+)-mandelic acid **man**. Two crystalline forms of the salt, **6aH$^+$ ·man$^-$** as the major product, and **(6aH$^+$·man$^-$)$_2$·man** as the minor product, were isolated and the amine’s absolute configuration was determined from their X-ray structures revealing the (1*R*)-configuration of the (−)-enantiomer in both crystal forms. The optically active amine was obtained with 93% ee after two crystallizations of the salt from chloroform. The nitrosation of the amines with HNO_2 gave nitrosamines **1b–4b** and (+)-**6b**. The oxidation of compound **6b** with trifluoroperacetic acid in CH_2Cl_2 was carried out according to a procedure reported by Emmons[12] to afford the *N*-nitramine (+)-**6c**.

The X-ray diffraction studies of *N*-nitrosamines **1b–4b** showed that the bicyclic skeleton adopts a twin-chair conformation stabilized by the aryl substituents at the equatorial positions (Fig. 1). The single crystals obtained by crystallization of the racemic compounds **1b–4b** showed that all of them crystallized in the chiral space group $P2_12_12_1$ indicating that a spontaneous resolution was achieved. The crystal structure of **1b** revealed that this compound forms homochiral crystals with each single crystal containing only one enantiomer. On the other hand, the structures of **2b**–**4b** showed that the nitroso group exhibits minor disorder assuming two orientations; however, the occupancy factors of the minor orientation are smaller than 0.120(3) in each case, thus indicating a significant preference of one enantiomer. The chirality of the above nitrosamines, resolved by a simple crystallization, was confirmed by their CD measurements.

The title compounds are rare examples of non-planar nitrosamine systems that, in contrast to the small ring compounds such as *N*-nitrosoaziridines,[13] are stable at room temperature, which makes them valuable models for spectroscopic investigation. The non-planarity of the nitrosamino chromophore is caused by the so called pseudoallylic $A^{(1,3)}$ strain, which in turn is caused by the strong steric interaction of the nearly coplanarly located two C atoms of the equatorial aryl substituents and the NNO group.[5,14] In order to avoid this strain, the molecules increase the pyramidal character of the amino nitrogen driving the NO group from the plane formed by the amino N-atom and the C-1 carbons of the aryl substituents. This was confirmed by the X-ray structures of **1b–4b** and **6b**, which revealed the displacement of the N-3 atom from the plane formed by the three neighboring atoms by 0.226–0.283 Å. A weakening of the $n_N–\pi_{NO}$ conjugation in the non-planar nitrosamino group results in a decreased barrier to the N–N rotation. In the case of **1b**–**4b** the corresponding activation energies are of the order of 13 kcal/mol and are almost half of those reported for simple nitrosamines (23–25 kcal/mol).[5,15] In effect, compounds **1b**–**3b** racemize instantly upon dissolution. Thus, their CD spectra can only be measured in the solid state. In contrast, nitrosamine **4b**, containing an asymmetrically substituted skeleton, is stereochemically stable in solution. The distortion of the chromophore from planarity results in a bathochromic shift of the n–π electronic transition[16] in the UV spectra of **1b**–**4b** and **6b** while the title compounds absorb near 410 nm in non-polar solvents as well as in the solid state, that is, at approximately 50 nm longer wavelengths than simple nitrosamines. The CD spectra of the compounds studied are collected in Table 1. The observed nitrosamine n–π Cotton

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Table 1
Circular dichroism (CD) data

Compd	Solvent	CD λ, nm ([Q])[a]
1b	KBr	433 (–2430), 372 (1040), 296 (2470) [b]
2b	KBr	448 (240), 403 (–2230), 309 (2370) [b]
3b	KBr	440 (80), 400 (–930) [b]
4b	Dioxan KBr	435 (–227), 387 (283) 438 (–520), 392 (1460) [b]
6b	MeOH KBr	425 (776), 375 (–1790), 263 (–6500) 430 (780), 385 (–1200) [b]
6c	MeOH	294 (–1180), 243 (18800)

[a] Molecular ellipticity in deg cm^2 $dmol^{-1}$.

[b] Approximate experimental values determined by considering the weight concentration (KBr density 2.75 g cm^{-3}).

effects (CEs) have a bisignate form in the solid state and also in solution, as in the case of **6b** (Figs. 2 and 3).

The CD spectra of **1b** and **2b** revealed two additional CD bands near 300 and 270 nm with a pronounced fine structure. The last band was also evident in the solution spectrum of **6b**. The 300 nm band can be assigned unequivocally to the ketone n–π electronic transition, whereas the second one probably corresponds to the aromatic ^1L_b transition, since the strong nitrosamine π–π absorption occurs at shorter wavelengths near 230 nm, which is usually structureless.[17] In order to establish the absolute configuration of **1b** and correlate it with the observed CE signs, we performed X-ray crystallographic analysis of three small pieces, that had been carefully cut from a large single crystal of this nitrosamine, and measured the solid state CD of the residual part. The absolute configuration was determined on the basis of the weak anomalous signals of the N, O, and F atoms. This resulted in a consistent indication of the *E*-configuration (geometric enantiomerism)[18] for all three pieces, thus minimizing the problem of possible racemic twinning of the crystal (see Experimental).

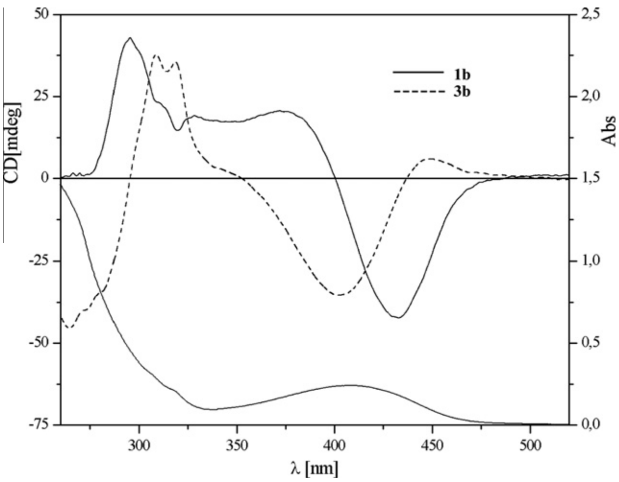

Figure 2. CD and UV–vis (lower curve) spectra of **1b** and **3b** measured in KBr disks.

A sample of *E*-**1b** showed a negative Cotton effect at 432 nm and a positive one at 378 nm; hence the configuration of the remaining nitrosamines crystallizing in the chiral space group can be assigned by comparison of their solid state CD spectra with those of **1b** in the region of the nitrosamine n–π transition. These assignments were also confirmed by the solution and solid state CD measurements for **6b**. This compound, which has a (1*R*)-configuration, showed a sequence of the positive and negative CEs at 425 and 380 nm, respectively in CH_2Cl_2 solution and the solid state. According to the ^1H NMR spectrum, the *anti*-rotamer predominates in the conformational equilibrium of **6b** in solution (the *syn/anti* ratio is 32:78), whereas in the solid state it is the only stereoisomer. In this case, the (1*R*)-configuration of the molecule with an *anti*-orientation of the nitroso group is equivalent to the *Z*-configuration of the geometric enantiomers of **1b**–**3b**. The observed CEs are rather strong, which points to an inherent chirality of the non-planar nitrosamine chromophore. The only exception is the solution spectrum of **4b** that showed a low magnitude of the CEs, apparently due to the almost equal population of the two rotamers (*syn/anti* 46:54) showing an opposite helicity of the chromophore. Thus, the n–π CE sign of the title nitrosamines can be simply predicted by a simple helicity rule: the chromophore twisted in the *P* sense, as in **1b** (the C–N–N═O torsion angle is 9.8°), should lead to a sequence of positive and negative CEs at higher and lower wavelengths. On the other hand, *M* chirality, as in **6b** (the C–N–N═O torsion angles in two independent molecules in the unit cell are of –9.4 and –8.6°), results in oppositely signed CEs being observed in solution as well as in the solid state.

The cause of the bisignate character of the CD curves in the region of the nitrosamine n–π transition is not clear. A similar form of the solution spectra, discussed earlier, in some *N*-nitrosopiperidines has been attributed to the equilibria of two or more ring conformers contributing to the CE with opposite signs.[4b] This is obviously impossible in the case of rigid bicyclic compounds, particularly in the solid state. In some cases, the bisignate CD may be attributed to a vibronic coupling effect.[19] According to Dekkers and Closs, a difference in the equilibrium geometry

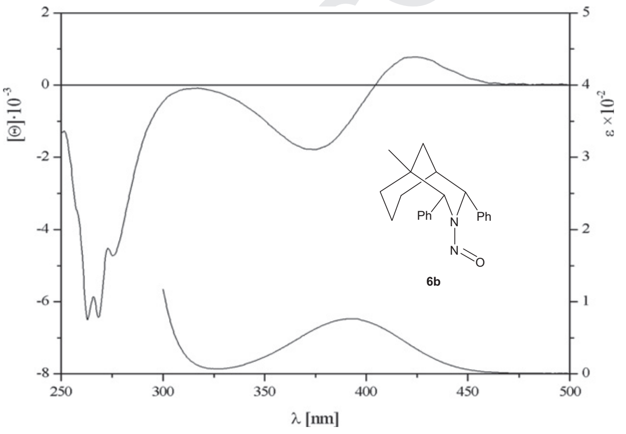

Figure 3. CD and UV–vis (lower curve) spectra of **6b** taken in methanol.

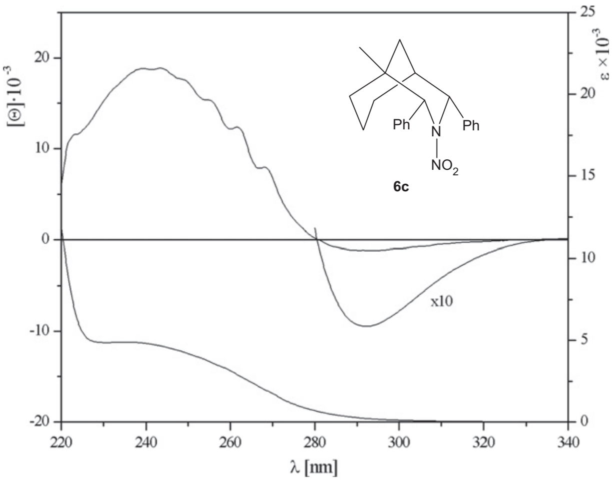

Figure 4. CD and UV–vis (lower curve) spectra of **6c** taken in methanol.

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between the ground and excited state of the molecule enables molecular vibrations to generate two oppositely signed components to the CE.[20] This seems to be a reasonable explanation for the compounds with a non-planar nitrosamine chromophore, which may easily change the geometry around the pyramidal amino nitrogen during the excitation.

The chromophore in nitramine **6c** is also deviated from planarity for the same reasons as the related nitrosamines. However in this case, it remains inherently symmetric (C_s) as shown by the crystal structure (the CNNO torsion angles are of 19.3 and −20.3° in the A molecule and 20.1 and −18.6° in the molecule B). Thus, the CE at 294 nm in the region of the nitramine n–π transition[10a,21] is relatively weak and monosignate, whereas the strong CD near 250 nm corresponds to overlapping nitramine π–π and aromatic ^1L_b transition (Fig. 4).

3. Conclusion

In conclusion, we have found that some easily accessible 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones crystallize as conglomerates and therefore by picking a suitable crystal, we were able to measure their chiroptical spectra. Simple crystallization is obviously the most economical procedure for obtaining chiral compounds. However, the spontaneous resolution is not a very frequent phenomenon, since most compounds show a great tendency to crystallize in centrosymmetric space groups. The *N*-nitroso-2,4-diaryl-3-azabicyclo[3.3.1]nonanes derived from symmetric amines rapidly racemize in solution and therefore their CD spectra must be taken in the solid state. A pyramidal character of the amino nitrogen caused by the pseudoallylic $A^{(1,3)}$ strain in these compounds causes an inherent chirality of the NNO chromophore that leads to strong bisignate Cotton effects in their CD spectra. The observed n–π CD signs are governed by the helicity of the non-planar nitrosamine group.

4. Experimental

4.1. General

Compounds **1a, 3a**, **5a,** and **1b** were prepared as described previously.[5,11] The ee of the amine (+)-**6a** was assigned by ^{1}H NMR measurements with the use of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid as the chiral solvating agent. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity Plus spectrometer at 500 and 125 MHz, respectively. Deuterated solvents were used as the internal lock for ^{1}H and ^{13}C NMR. The solid state CD spectra were taken with freshly prepared KBr disks and recorded with a Jasco J-715 dichrograph. A mixture of 2–5 mg of the sample and 250 mg of dried KBr was ground and formed into a disk 0.5 mm thick and with radius of 15 mm. The disk was rotated around the optical axis and the CD recordings were made for several positions in order to check the reproducibility of the spectra. Caution: All nitrosamines are potential chemical carcinogens, and special care should be taken in the handling and disposal of these substances.[22]

4.2. 2,4-Bis(2-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one 2a

A solution of ammonium acetate (1.9 g, 25 mmol), *o*-tolualdehyde (6.0 mL, 50 mmol) and cyclohexanone (3.5 mL, 35 mmol) in methanol (25 mL) was left to stand for 24 h at room temperature. The precipitated crystals were filtered, washed with methanol, and recrystallized from toluene-heptane: yield 3.1 g (35%); mp 225–226 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.19 (m, 4H), 4.59 (s, 2H), 3.02 (m, 1H), 2.51 (s, 2H), 2.35 (s, 6H), 1.99 (m, 1H), 1.78 (m, 2H), 1.61 (s, 1H), 1.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 217.8, 139.0, 134.8, 130.8, 127.2, 125.9, 61.3, 50.7, 29.3, 21.0, 19.1; Anal. Calcd for $C_{22}H_{25}NO$ (319): C, 82.7; H, 7.9; N, 4.4. Found: C, 82.8; H, 7.8; N, 4.5.

4.3. 1-Methyl-2,4-bis(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one 4a

Obtained in a manner similar to that of compound **2a**; mp 143–144 °C (toluene–heptane); ^{1}H NMR ($CDCl_3$) δ 7.48 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 6.92 (m, 4H), 4.34 (d, *J* = 2.9 Hz, 1H), 3.89 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.16 (m, 1H), 2.51 (s, 1H), 2.08 (m, 1H), 1.97 (m, 1H), 1.82 (s, 1H), 1.72 (m, 1H), 1.45 (m, 2H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.1, 159.2, 158.8, 133.4, 132.0, 130.0, 127.8, 113.8, 113.3, 64.4, 55.2, 54.6, 50.9, 29.0, 21.4, 20.3; Anal. Calcd for $C_{23}H_{27}NO_3$ (365): C, 75.6; H, 7.5; N, 3.8. Found: C,75.5; H, 7.5; N, 3.8.

4.4. (1*R*)-1-Methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonane 6a

Racemic amine **6a** (5.1 g, 15 mmol) and (+)-mandelic acid (2.3 g, 15 mmol) were dissolved in hot toluene (25 ml). The precipitated salt was recrystallized from hot toluene. The crystalline salt was treated with 10% aqueous solution of NaOH and extracted with benzene. After evaporation of the solvent the residue was recrystallized from methanol to obtain 1.6 g of the product, mp 111–112 °C (racemate lit.[5] mp 128–129 °C); $[\alpha]_D^{22}$ = +26.2 (*c* 4, C_6H_6); ee 93%.

4.5. *N*-Nitroso-2,4-bis(2-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one 2b

To a solution of amine **2a** (1.60 g, 5 mmol) in chloroform (10 mL) were added concentrated hydrochloric acid (1.5 mL) and water (1.5 mL), and while stirring, solid $NaNO_2$ (0.84 g, 12 mmol) was added in portions over 0.5 h. The stirring was continued for another 0.5 h. The organic layer was washed with water and saturated $NaHCO_3$ and dried (Na_2SO_4). After evaporation of the solvent, the residue was crystallized from toluene–heptane: yield 1.45 g (78%); mp 197–198 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.8–7.4 (br, 2H), 7.26 (m, 6H), 5.62 (br, 2H), 2.92 (s, 2H), 2.42 (s, 6H), 2.28 (m, 1H), 1.77 (m, 4H), 1.47 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 213.3, 135.6 (br), 133.4 (br), 131.5, 127.9, 127.4, 125.9, 64.2 (br), 48.2, 30.2, 19.2, 18.4; Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348): C, 75.8; H, 6.9; N, 8.0. Found: C, 75.5; H, 7.0; N, 8.0.

4.6. *N*-Nitroso-2,4-bis(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one 3b

Obtained in a manner similar to that of compound **2b**; mp 166–169 °C dec (CH_2Cl_2–MeOH); ^{1}H NMR ($CDCl_3$) δ 7.40–7.10 (br, 4H), 6.96 (m, 4H), 5.42 (br, 1H), 3.83 (s, 6H), 2.83 (m, 2H), 1.99 (m, 1H), 1.75 (m, 1H), 1.70 (m, 2H), 1.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 213.1, 158.7, 130.2, 129.6 (br), 126.4 (br), 114.1, 63.5 (br), 55.2, 51.5, 29.9, 18.1; Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380): C, 69.5; H, 6.4; N, 7.4. Found: C, 69.4; H, 6.5; N 7.1.

4.7. *N*-Nitroso-1- methyl-2,4-bis(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one 4b

Obtained in a manner similar to that of compound **2b**; mp 156–159 °C dec (CH_2Cl_2–MeOH); ^{1}H NMR ($CDCl_3$) δ 7.44 (br, 2H), 7.10 (br, 2H), 6.95 (m, 4H), 5.29 (br, 1H), 5.05 (br, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.93 (m, 1H), 2.24 (m, 1H), 1.97 (m, 1H), 1.73 (m, 2H), 1.47 (m, 2H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.3, 159.5,

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159.1, 130.2, 129.6 (br), 129.2, 126.4 (br), 114.3, 114.1, 74.5 (br), 65.5 (br), 55.5, 51.3, 50.0, 37.6, 30.5, 21.8, 19.5; Anal. Calcd for $C_{23}H_{26}N_2O_4$ (394): C, 70.0; H, 6.6; N, 7.1. Found: C, 69.8; H, 6.6; N, 7.0.

4.8. (1*R*)-N-Nitroso-1-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonane 6b

Obtained in a manner similar to that of compound **2b**; mp 173–174 °C (CH_2Cl_2–MeOH) (racemate lit.[5] mp 139 °C); $[\alpha]_D^{22}$ = +36.5 (*c* 2.3, C_6H_6).

4.9. (1*R*)-*N*-Nitro-1-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonane 6c

To 80% of hydrogen peroxide (0.4 mL) suspended in 5 mL of methylene chloride (5 mL) with stirring was added trifluoroacetic anhydride (2 mL) under a reflux condenser. After the vigorous reaction ceased, a solution of peroxytrifluoroacetic acid (2.5 mL) was added dropwise to nitrosoamine **6b** (0.64 g, 2 mmol) in methylene chloride (10 mL). The reaction mixture was left to stand overnight at room temperature. The organic layer was washed with water and saturated $NaHCO_3$ and dried (Na_2SO_4). After evaporation of the solvent, the residue was subjected to column chromatography on silica gel, and elution with $CHCl_3$ gave 0.35 g (52%) of the product crystallized from CH_2Cl_2–MeOH; mp 180–181 °C dec ($[\alpha]_D^{22}$ +68.6 (*c* 3, C_6H_6); ^1H NMR ($CDCl_3$) δ 7.60–7.25 (complex m, 10 H), 5.34 (d, *J* = 6.8 Hz, 1H), 4.88 (s, 1H), 2.64 (m, 1H), 1.91 (m, 1H), 1.74 (m, 2H), 1.30 (m, 1H), 1.24 (m, 2H), 1.14 (m, 1H) 1.10 (s, 3H), 0.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.3, 139.8, 128,5, 128.0, 127.0, 126.5, 124.4, 76.5, 69.2, 38.8, 35.8, 35.5, 33.9, 30.8, 26.4, 19.7; Anal. Calcd for $C_{21}H_{24}N_2$O2 (394): C, 75.0; H, 7.2; N, 8.3. Found: C, 74.7; H, 7.2; N, 8.3.

4.10. X-Ray crystal structure analyses

The X-ray intensity data were collected with a four-circle KM4 diffractometer using Mo Kα radiation [**6a**H^+-(*S*)-(+)-mandelate] or Cu Kα radiation **6b** and with an Oxford Diffraction SuperNova diffractometer using Cu Kα radiation **1b**–**4b**, **6c**, bis[**6a**H^+-(*S*)-(+)-mandelate]-mandelic acid. The crystal structures were solved by direct methods with SHELXS97[23] and refined by full-matrix least-squares SHELXL97.[23] All hydrogen atoms were refined as riding on their carriers and their displacement parameters were set equal to $1.5U_{eq}(C)$ for the methyl groups and $1.2U_{eq}(C)$ for the remaining H atoms.

Two factors could influence the enantiopurity of the crystals studied, the disorder of the NNO group and racemic twinning. Therefore a special care was taken in order to identify any possible signs of disorder of the nitroso groups by analyzing the final electron-density difference maps and the shape of the displacement ellipsoids of the nitrosamine N and O atoms. In the case of **1b**, where due to the presence of F atoms, the strongest anomalous signal could be obtained, in order to rule out the possibility of racemic twinning, three data sets with a very large redundancy were collected from three small crystals cut from a larger well-shaped specimen. In each case, a nearly identical value of the Flack parameter was obtained with an s.u. value of 0.10 indicating the same absolute structure over the crystal. Moreover the fourth data set was collected from a different crystal taken from the same crystallization batch for which the opposite absolute structure was determined based on the value of the Flack parameter[24] $x = 0.05(11)$. Based on the above data, despite a rather high s.u. value of the Flack parameter, enantiopurity of the crystals of **1b** was assumed. In turn, for the crystals of **2b** and **4b**, X-ray diffraction data did not allow us to rule out the possibility of their twinning by inversion.

Crystal data for $C_{22}H_{20}F_4N_2O_2$ **1b**: orthorhombic, space group $P2_12_12_1$, $a = 7.8736(1)$, $b = 11.3831(1)$, $c = 21.7311(1)$ Å, $V = 1947.67(3)$ Å^3, $Z = 4$, $\lambda = 1.54184$ Å, $T = 293$ K, number of measured reflections 155721, $R_{int} = 0.0434$, $R_1 = 0.0300$, $wR_2 = 0.0866$ for 4072 independent reflections with $I > 2\sigma(I)$, Flack parameter[24] $x = -0.01(10)$.

Crystal data for $C_{22}H_{24}N_2O_2$ **2b**: orthorhombic, space group $P2_12_12_1$, $a = 6.9909(1)$, $b = 8.0891(2)$, $c = 33.0085(7)$ Å, $V = 1866.63(7)$ Å^3, $Z = 4$, $\lambda = 1.54184$ Å, $T = 293$ K, number of measured reflections 41905, $R_{int} = 0.0207$, $R_1 = 0.0354$, $wR_2 = 0.0957$ for 3897 independent reflections with $I > 2\sigma(I)$. The absolute structure could not be reliably assigned as the Flack parameter[24] s.u. value was too high [$x = 0.0(3)$]. The nitroso group that is disordered over two positions was refined with restraints imposed on its geometry. The occupancy factor of the minor position is 0.119(2).

Crystal data for $C_{22}H_{24}N_2O_4$ **3b**: orthorhombic, space group $P2_12_12_1$, $a = 7.5779(2)$, $b = 10.8891(3)$, $c = 22.9360(6)$ Å, $V = 1892.60(9)$ Å^3, $Z = 4$, $\lambda = 1.54184$ Å, $T = 293$ K, number of measured reflections 43543, $R_{int} = 0.0467$, $R_1 = 0.0307$, $wR_2 = 0.0805$ for 3822 independent reflections with $I > 2\sigma(I)$, Flack parameter[24] $x = -0.04(17)$. The nitroso group that is disordered over two positions was refined with restraints imposed on its geometry. The occupancy factor of the minor position is 0.073(2).

Crystal data for $C_{23}H_{26}N_2O_4$ **4b**: orthorhombic, space group $P2_12_12_1$, $a = 8.1311(1)$, $b = 11.3597(1)$, $c = 22.1609(2)$ Å, $V = 2046.93(4)$ Å^3, $Z = 4$, $\lambda = 1.54184$ Å, $T = 293$ K, number of measured reflections 15561, $R_{int} = 0.0175$, $R_1 = 0.0323$, $wR_2 = 0.0895$ for 4235 independent reflections with $I > 2\sigma(I)$. The absolute structure could not be reliably assigned as the Flack parameter[24] value was $x = 0.39(18)$. The nitroso group that is disordered over two positions was refined with restraints imposed on its geometry. The occupancy factor of the minor position is 0.109(3).

Crystal data for $C_{21}H_{24}N_2O$ **6b**: monoclinic, space group $P2_1$, $a = 11.483(2)$, $b = 7.6774(1)$, $c = 11.996(2)$ Å, β = 96.50(3)°, $V = 1768.6(6)$ Å^3, $Z = 4$, $\lambda = 1.54184$ Å, $T = 293$ K, number of measured reflections 3172, $R_{int} = 0.0239$, $R_1 = 0.0334$, $wR_2 = 0.0929$ for 3042 independent reflections with $I > 2\sigma(I)$.

Crystal data for $C_{21}H_{24}N_2O_2$ **6c**: monoclinic, space group $P2_1$, $a = 12.3866(1)$, $b = 12.922(3)$, $c = 19.2324(1)$ Å, β = 94.536(1)°, $V = 1823.21(3)$ Å^3, $Z = 4$, $\lambda = 1.54184$ Å, $T = 294$ K, number of measured reflections 85585, $R_{int} = 0.0298$, $R_1 = 0.0331$, $wR_2 = 0.0919$ for 7297 independent reflections with $I > 2\sigma(I)$. For this compound with known absolute configuration the Flack parameter[24] value was $x = 0.09(14)$

Crystal data for $C_{21}H_{26}N{\cdot}C_8H_7O_3$ **6a**H^+-(*S*)-(+)-mandelate: orthorhombic, space group $P2_12_12_1$, $a = 10.045(2)$, $b = 10.990(2)$, $c = 21.689(4)$ Å, $V = 2394.3(8)$ Å^3, $Z = 4$, $\lambda = 0.71073$ Å, number of measured reflections 2166, $T = 293$ K, $R_1 = 0.0432$, $wR_2 = 0.1020$ for 2166 independent reflections with $I > 2\sigma(I)$. The absolute configuration of **6a**H^+ determined as 1*R* relative to the known configuration of (*S*)-(+)mandelate.

Crystal data for $2(C_{21}H_{26}N){\cdot}2(C_8H_7O_3){\cdot}(C_8H_8O_3)$ bis[**6a**H^+-(*S*)-(+)-mandelate]-mandelic acid: monoclinic, space group $P2_1$, $a = 10.1226(2)$, $b = 20.7144(5)$, $c = 13.9086(3)$ Å, $\beta = 105.756(2)$°, $V = 2806.83(11)$ Å^3, $Z = 4$, $\lambda = 1.54178$ Å, $T = 296$ K, number of measured reflections 21764, $R_{int} = 0.0180$, $R_1 = 0.0469$, $wR_2 = 0.1323$ for 10397 independent reflections with $I > 2\sigma(I)$, Flack parameter[24] $x = -0.04(16)$. The absolute configuration of **6a**H^+ was determined as (1*R*)-relative to the known configuration of (*S*)-(+)-mandelate.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 857277–857284. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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