69. Absolute Configuration of 2-Substituted 2-Azabicyclo[2.2.1]hept-5-enes

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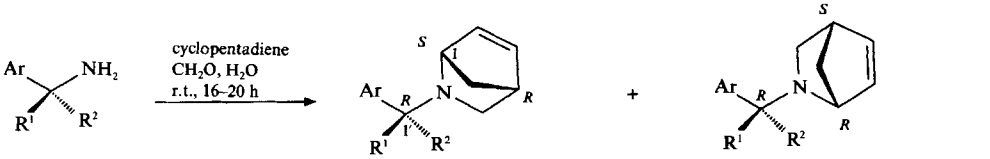
The diastereoisomeric 2-substituted 2-azabicyclo[2.2.1]hept-5-enes **2–4** were prepared by aza-*Diels-Alder* reaction of cyclopentadiene with the corresponding methaniminium ions. Their relative configurations were deduced using $^1H,^1H$-ROESY experiments, and their absolute configurations were assigned from the crystal structure of the aziridinium derivative (–)-**5**. The absolute configuration of (+)-**1**, *i.e.* (1*R*), was assigned by CD spectroscopy.

Introduction. – Following *Grieco* and *Larsen*'s pioneering report of the aza-*Diels-Alder* reaction between cyclopentadiene and *N*-benzylmethaniminium ion, formed *in situ* in aqueous medium [1], many groups exploited and extended this reaction [2]. Analogous diastereoselective reactions were described using amino acids [3] [4] as chiral sources.

The absolute configurations of the aza-*Diels-Alder* adducts with chiral 1-phenylethylamine were, however, unknown. In the course of our syntheses of muscarinic agonists [5] and terpene alkaloids [6], we needed the aza-*Diels-Alder* adducts in enantiomerically pure form and knowledge of their absolute configuration. Thus, we assigned the relative configurations of the adducts using 2D-ROESY experiments and confirmed the validity of the NMR method by independent assignment of the absolute configuration of aziridinium bromide (–)-**5** by X-ray crystallography. With this knowledge in hand, the absolute configurations of the enantiomers of **1** could be deduced by CD spectroscopy.

Results and Discussion. – *Synthesis.* Following an analogous procedure to that originally described [1], the compounds **1–4** were synthesized by *in situ* reaction of the corresponding benzylamine hydrochloride with formaldehyde and cyclopentadiene (*Scheme 1*). The ratio of diastereoisomers (–)-**2a**/(+)-**2b**, (–)-**3a**/(–)-**3b**, and (+)-**4a**/(–)-

Scheme 1. *Aza*-Diels-Alder *Reaction with Benzylamines*



(–)-**1** Ar = Ph, $R^1 = R^2 = H$
(–)-**2a** Ar = Ph, $R^1 = H$, $R^2 = Me$
(+)-**3a** Ar = 4-BrC_6H_4, $R^1 = H$, $R^2 = Me^a)$
(+)-**4a** Ar = 4-$NO_2C_6H_4$, $R^1 = H$, $R^2 = Me$

(+)-**1** Ar = Ph, $R^1 = R^2 = H$
(+)-**2b** Ar = Ph, $R^1 = H$, $R^2 = Me$
(+)-**3b** Ar = 4-BrC_6H_4, $R^1 = H$, $R^2 = Me^a)$
(–)-**4b** Ar = 4-$NO_2C_6H_4$, $R^1 = H$, $R^2 = Me$

[a]) In fact, the corresponding enantiomer was prepared.

4b was determined directly after workup from the 360-MHz ^{1}H-NMR spectrum of the crude product mixture, and the diastereoisomers were then separated by chromatography.

*Conformation and Configuration of the Aza-*Diels-Alder *Adducts* **2–4**. *Waldmann* [3] [7] assigned the relative configurations of the adducts arising from aza-*Diels-Alder* reactions with methanimines from L-amino acids using ^{1}H-NMR nuclear *Overhauser* effect (NOE) experiments. We applied an analogous methodology to determine the relative configurations of adducts **2–4**, using 2D rotating-frame nuclear *Overhauser* spectroscopy (^{1}H,^{1}H-ROESY) [8] experiments. Three *gauche* conformations are possible for both diastereoisomers (–)-**2a** and (+)-**2b** (obtained from (+)-(*R*)-1-phenylethylamine), when the phenylethyl moiety is in an *endo*-position (*Fig. 1*, **A**–**C** and **D**–**F**, resp.). Of particular interest to

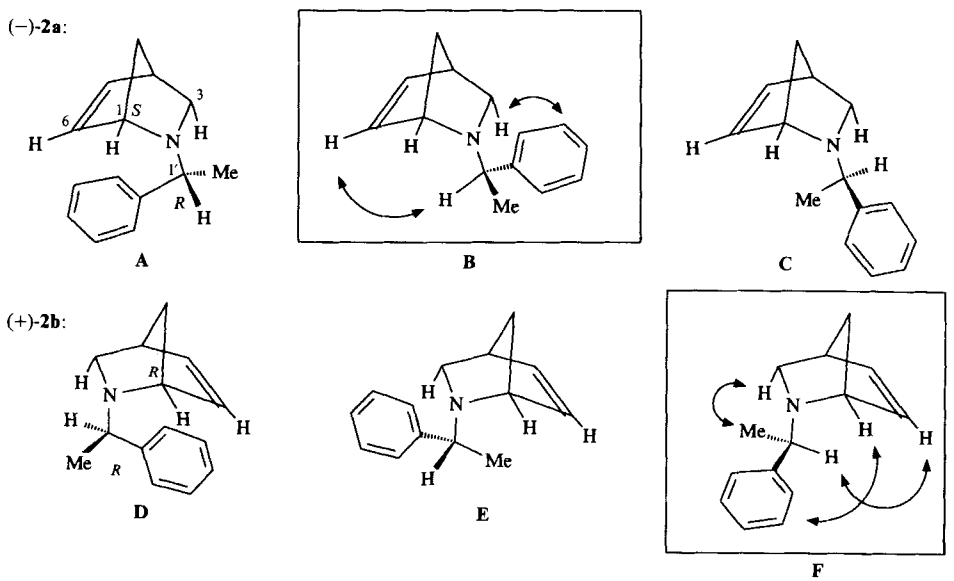


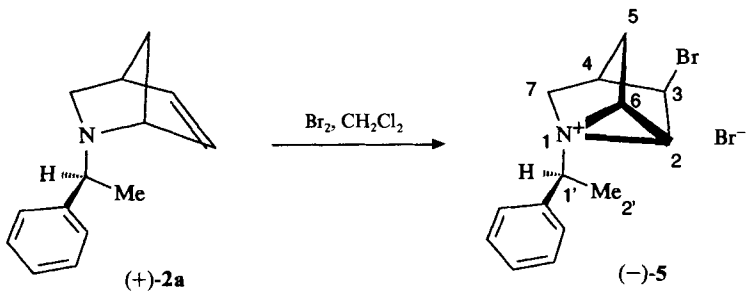
Fig. 1. *Low-energy conformations of* (–)-**2a** *and* (+)-**2b** *and some observed NOE's*

the assignment of the relative configuration are the NOE's between the substituent at N(2) and the bicyclic nucleus (see *Fig. 1*), suggesting conformation **B** for (–)-**2a** and **F** for (+)-**2b**. The NOE method, however, assumes one highly preferred conformation in solution, and this assumption is not always valid, especially not in the case of bonds subject to free rotation [9]. In fact, the observed NOE's can equally be explained by the coexistence of 2 main conformations in solution, namely **A** and **B** for (+)-**2b** and **E** and **F** for (–)-**2a**, which would result in the opposite relative configuration to that assigned.

For the minor diastereoisomer (+)-**2b**, NOE cross peaks are seen between the benzylic H–C(1′) and the olefinic H at C(6). This is satisfied only by conformations, **B** and **F**. Me–C(1′) shows a NOE with H_{endo}–C(3), thus excluding **B**. Additionally, a cross peak is seen between the aromatic protons and H–C(1), providing further evidence for **F**. This assignment is confirmed by the major diastereoisomer (–)-**2a** which shows a NOE between H–C(1′) and H–C(6), compatible only with conformations **B** and **F**. The aromatic protons of (–)-**2a** present a NOE with H_{endo}–C(3), thus indicating that the major stereoisomer adapts conformation **B**.

To obtain an independent and unambiguous assignment of the absolute configuration, the main diastereoisomer (+)-**2a** obtained from the reaction of (−)-(*S*)-1-phenylethylamine, aqueous formaldehyde, and cyclopentadiene, was converted to the aziridinium salt (−)-**5** by treatment with Br_2 in CH_2Cl_2 (*Scheme 2*). The crystal structure of (−)-**5** (see *Fig. 2*) was solved by conventional methods and its absolute configuration independently assigned using the method described by *Boelsterli et al.* [10]. Thus, the absolute configuration of (+)-**2a** is (1*R*,1′*S*), which confirms the relative configuration assigned to its enantiomer (−)-**2a** using the ROESY procedure (see above).

Scheme 2



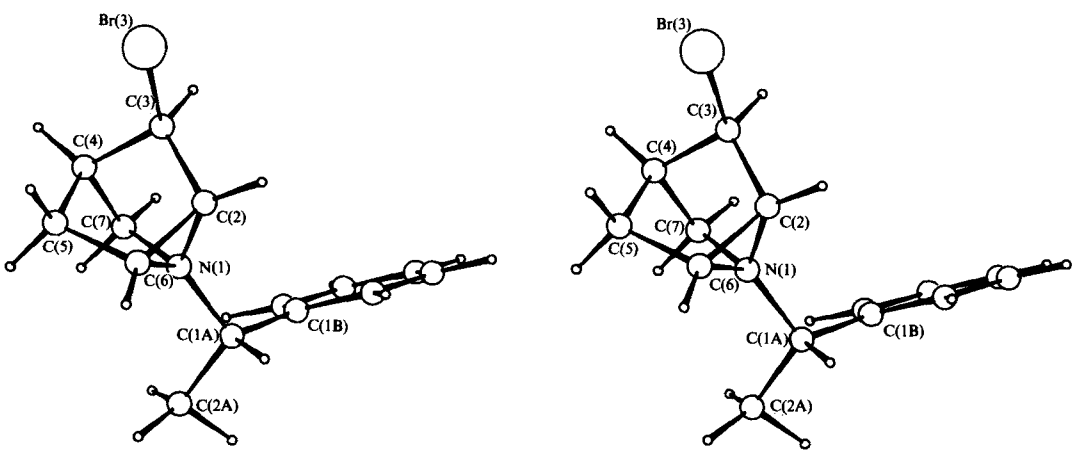


Fig. 2. *Crossed stereoscopic view of the crystal structure of (−)-***5**, *derived from (S)-1-phenylethylamine*

Aziridinium salts analogous to (−)-**5** were previously prepared [11], but to our knowledge, no crystal structure of such compounds was reported. Selected bond lengths, angles, and torsion angles of (−)-**5** are given in the *Table*. The bond lengths for the aziridinium-ion moiety are 1.508 (N–C(6)), 1.500 (N–C(2)), and 1.496 Å (C(2)–C(6)), all practically the same within the standard deviation. However, the C(2)–C(6) bond is the shortest C–C bond of (−)-**5**, as the others range from 1.511 to 1.528 Å. The lengthening of N–C bonds (normal average value 1.46 Å) and the shortening of C–C bonds (normal average

Table. *Selected Bond Lengths, Bond Angles, and Torsion Angles for the Crystal Structure of* (−)-**5**. Standard deviations in parentheses.

Bond lengths [Å]			
Br(3)–C(3)	1.945 (7)	C(3)–C(4)	1.528 (10)
N(1)–C(2)	1.500 (9)	C(4)–C(5)	1.526 (10)
N(1)–C(6)	1.508 (9)	C(4)–C(7)	1.526 (10)
N(1)–C(7)	1.497 (9)	C(5)–C(6)	1.512 (10)
N(1)–C(1A)	1.490 (9)	C(1A)–C(2A)	1.511 (12)
C(2)–C(3)	1.516 (10)	C(1A)–C(1B)	1.508 (10)
C(2)–C(6)	1.496 (10)		
Angles [°]			
C(2)–N(1)–C(6)	59.7 (4)	C(2)–C(3)–C(4)	97.8 (5)
C(2)–N(1)–C(7)	107.2 (5)	C(3)–C(4)–C(5)	104.6 (6)
C(2)–N(1)–C(1A)	121.6 (5)	C(3)–C(4)–C(7)	98.5 (5)
C(6)–N(1)–C(7)	107.3 (5)	C(5)–C(4)–C(7)	101.4 (6)
C(6)–N(1)–C(1A)	119.4 (5)	C(4)–C(5)–C(6)	96.7 (6)
C(7)–N(1)–C(1A)	124.2 (5)	N(1)–C(6)–C(2)	59.9 (4)
N(1)–C(2)–C(3)	104.1 (5)	N(1)–C(6)–C(5)	105.7 (5)
N(1)–C(2)–C(6)	60.4 (4)	C(2)–C(6)–C(5)	108.8 (6)
C(3)–C(2)–C(6)	106.7 (6)	N(1)–C(7)–C(4)	97.2 (5)
Br(3)–C(3)–C(2)	110.1 (5)	N(1)–C(1A)–C(2A)	108.8 (6)
Br(3)–C(3)–C(4)	114.3 (5)	N(1)–C(1A)–C(1B)	111.0 (6)
Torsion angles [°]			
C(6)–N(1)–C(2)–C(3)	−101.4 (6)	N(1)–C(2)–C(3)–Br(3)	154.1 (4)
C(7)–N(1)–C(2)–C(3)	−1.0 (6)	N(1)–C(2)–C(3)–C(4)	34.6 (6)
C(7)–N(1)–C(2)–C(6)	100.4 (5)	C(6)–C(2)–C(3)–Br(3)	91.3 (6)
C(1A)–N(1)–C(2)–C(3)	150.7 (6)	C(6)–C(2)–C(3)–C(4)	−28.2 (7)
C(1A)–N(1)–C(2)–C(6)	−107.9 (6)	N(1)–C(2)–C(6)–C(5)	−97.6 (6)
C(2)–N(1)–C(6)–C(5)	102.9 (6)	C(3)–C(2)–C(6)–N(1)	97.1 (6)
C(7)–N(1)–C(6)–C(2)	−100.2 (5)	C(3)–C(2)–C(6)–C(5)	−0.5 (7)
C(7)–N(1)–C(6)–C(5)	2.8 (7)	Br(3)–C(3)–C(4)–C(5)	−67.9 (6)
C(1A)–N(1)–C(6)–C(2)	111.5 (6)	Br(3)–C(3)–C(4)–C(7)	−172.1 (4)
C(1A)–N(1)–C(6)–C(5)	−145.5 (6)	C(2)–C(3)–C(4)–C(5)	48.4 (6)
C(2)–N(1)–C(7)–C(4)	−33.1 (6)	C(2)–C(3)–C(4)–C(7)	−55.8 (6)
C(6)–N(1)–C(7)–C(4)	29.7 (6)	C(3)–C(4)–C(5)–C(6)	−48.1 (6)
C(1A)–N(1)–C(7)–C(4)	176.1 (6)	C(7)–C(4)–C(5)–C(6)	53.9 (6)
C(2)–N(1)–C(1A)–C(2A)	154.0 (6)	C(3)–C(4)–C(7)–N(1)	54.7 (6)
C(2)–N(1)–C(1A)–C(1B)	−78.3 (7)	C(5)–C(4)–C(7)–N(1)	−52.2 (6)
C(6)–N(1)–C(1A)–C(2A)	83.5 (7)	C(4)–C(5)–C(6)–N(1)	−34.0 (6)
C(6)–N(1)–C(1A)–C(1B)	−148.8 (6)	C(4)–C(5)–C(6)–C(2)	29.0 (7)
C(7)–N(1)–C(1A)–C(2A)	−59.2 (8)	N(1)–C(1A)–C(1B)–C(2B)	97.8 (8)
C(7)–N(1)–C(1A)–C(1B)	68.5 (8)	N(1)–C(1A)–C(1B)–C(6B)	−84.1 (9)

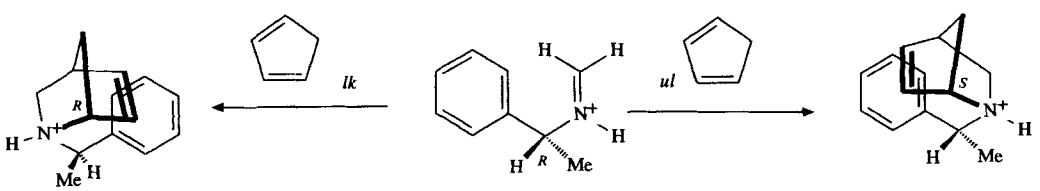
value 1.54 Å) is usually observed in aziridines [12]. The N–C bonds of (−)-**5**, however, are unusually long, either due to the strain of the tricyclic structure or to the effect of the charge on the N-atom. The Br-atom at C(3) effectively shields the aziridinium moiety from nucleophilic attack at C(2), which occurs on C(6) with a variety of nucleophiles under cleavage of the already lengthened N–C(6) bond [5] and inversion of configuration.

Having gained increased confidence in the assignment of relative configuration by ^{1}H-NMR, an analogous ROESY procedure was employed to assign the relative configu-

ration of the crystalline diastereoisomeric adducts obtained from the aza-*Diels-Alder* reaction using (−)-(*S*)-1-(4-bromophenyl)ethylamine. Thus, (1*R*,1′*S*) (*u*) configuration was established for (−)-**3a** (NOE's: Me−C(1′)/H_{endo}−C(3), H−C(1′)/H−C(6)) and (1*S*,1′*S*) (*l*) configuration for its corresponding diastereoisomer (−)-**3b** (NOE's: Me−C(1′)/H−C(6), H−C(1′)/H−C(6), arom. H's/H_{endo}−C(3)). The relative configurations of the adducts (+)-**4a** and (−)-**4b** derived from (+)-(*R*)-1-(4-nitrophenyl)ethylamine were also readily assigned, thus establishing the configurations (1*S*,1′*R*) and (1*R*,1′*R*), respectively (NOE's of (+)-**4a**: Me−C(1′)/H−C(1), Me−C(1′)/H−C(6), H−C(1′)/H−C(6), arom. H/H_{endo}−C(3) (small); NOE's of (−)-**4b**: H_{endo}−C(3)/(Me−C(1′), H−C(6)/H−C(1′), arom. H/H−C(1)).

Factors Affecting Stereoselectivity. The diastereoselectivity of the reaction between cyclopentadiene and the protonated (*R*)-*N*-(1′-phenylethyl)methanimine can be rationalised in terms of two competing *endo*-transition states (*lk* and *ul*), where the iminium ion is in an s-*cis*-conformation (as shown in *Scheme 3*) and, therefore, approach of the diene to the *Re* face of the iminium ion (*lk*) is disfavoured due to steric interactions with Me−C(1′), thus leading to the (1*S*,1′*R*)-isomer as the main product[1]).

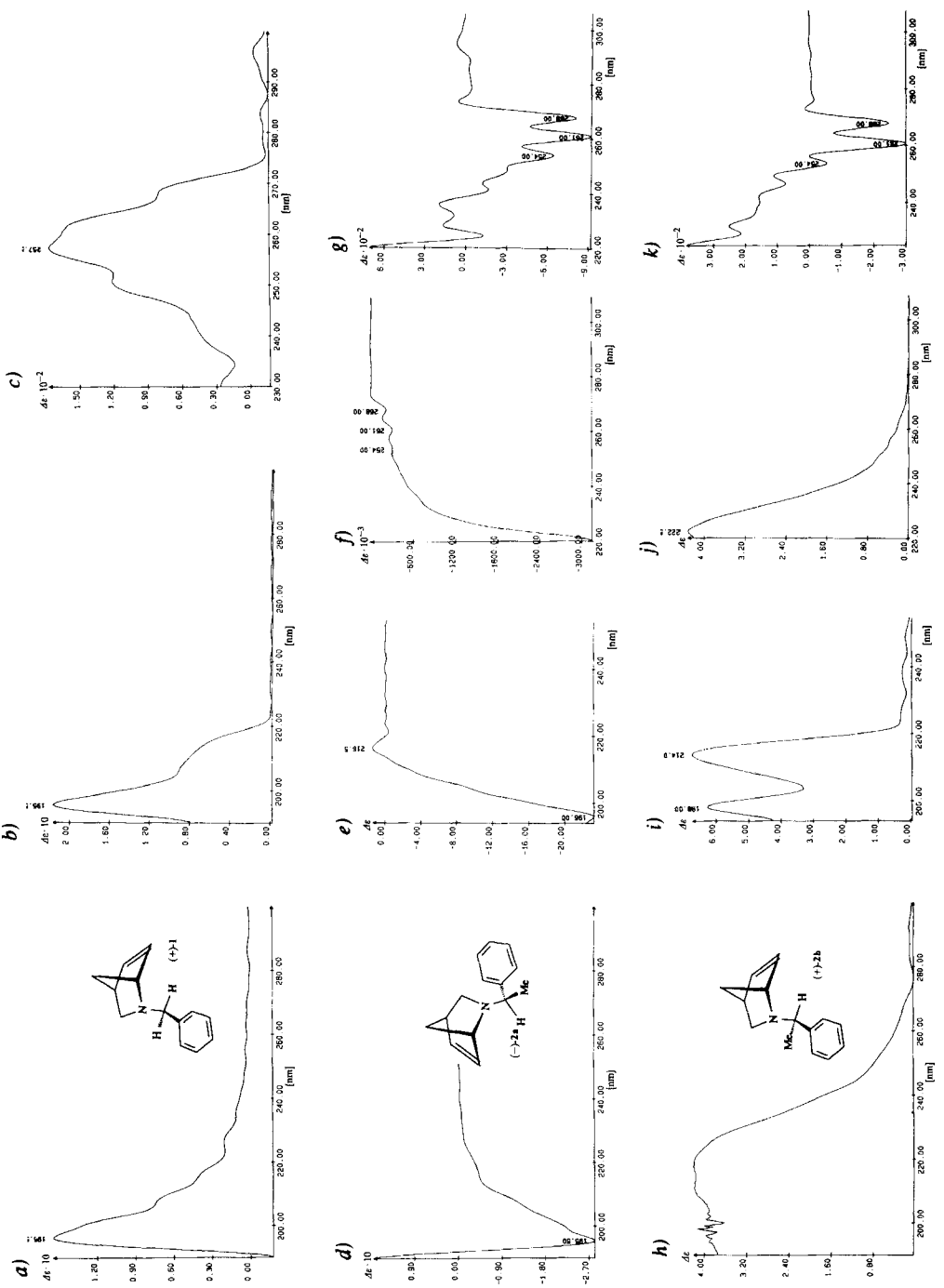
Scheme 3. *Relative Topicity of the Aza-*Diels-Alder *Addition to the Chiral Methaniminium Ion*



The aza-*Diels-Alder* reaction is rather sensitive to electronic and steric parameters. Although the reaction with (*S*)-1-phenylethylamine gave a 3:1 *ul*/*lk* ratio, substitution at the 4-position of Ph with either a Br or a NO_2 group resulted in a much lower selectivity. Thus, under comparable conditions, with (*S*)-1-(4-bromophenyl)ethylamine, a ratio of 1.4:1 *ul*/*lk* addition (*i.e.* (−)-**3a** (1*R*,1′*S*)/(−)-**3b** (1*S*,1′*S*)) and with (*R*)-1-(4-nitrophenyl)ethylamine, a ratio of 1.2:1 *ul*/*lk* addition (*i.e.* (+)-**4a** (1*S*,1′*R*)/(−)-**4b** (1*R*,1′*R*)) was observed. Presumably, both *para*-substitutions lead to a looser transition state, in which the steric demand of Me−C(1′) is less pronounced than in the unsubstituted aromatic analogue.

Somewhat surprisingly, an Et group at the benzylic position C(1′) also results in loss of stereoselectivity. Using (−)-1-phenylpropylamine, a 1:1 ratio of diastereoisomers, *i.e.* no stereoselectivity, was observed. With ethyl (−)-(*R*)-2-amino-2-phenylacetate, a 1:4 ratio of diastereoisomers was obtained [13]. It remains to be seen whether bulkier substituents at C(1′) of benzylamines will provide enhanced diastereoselectivity in this reaction. However, the assumption that two competing *endo*-transition states (see *Scheme 3*) is sufficient to explain the selectivities observed may be inappropriate. Other

[1]) To avoid confusion, it is emphasised that *ul* and *lk* refer to additions to a particular face of the corresponding methaniminium ion. Thus, for discussion of the stereoselectivity of this reaction, we shall refer to relative topicity of the addition, rather than to the relative topicity of the products (denoted *u* and *l*).


a)
b)
c)
d)
e)
f)
g)
h)
i)
j)
k)
(+)-1
(−)-2a
(+)-2b
[nm]

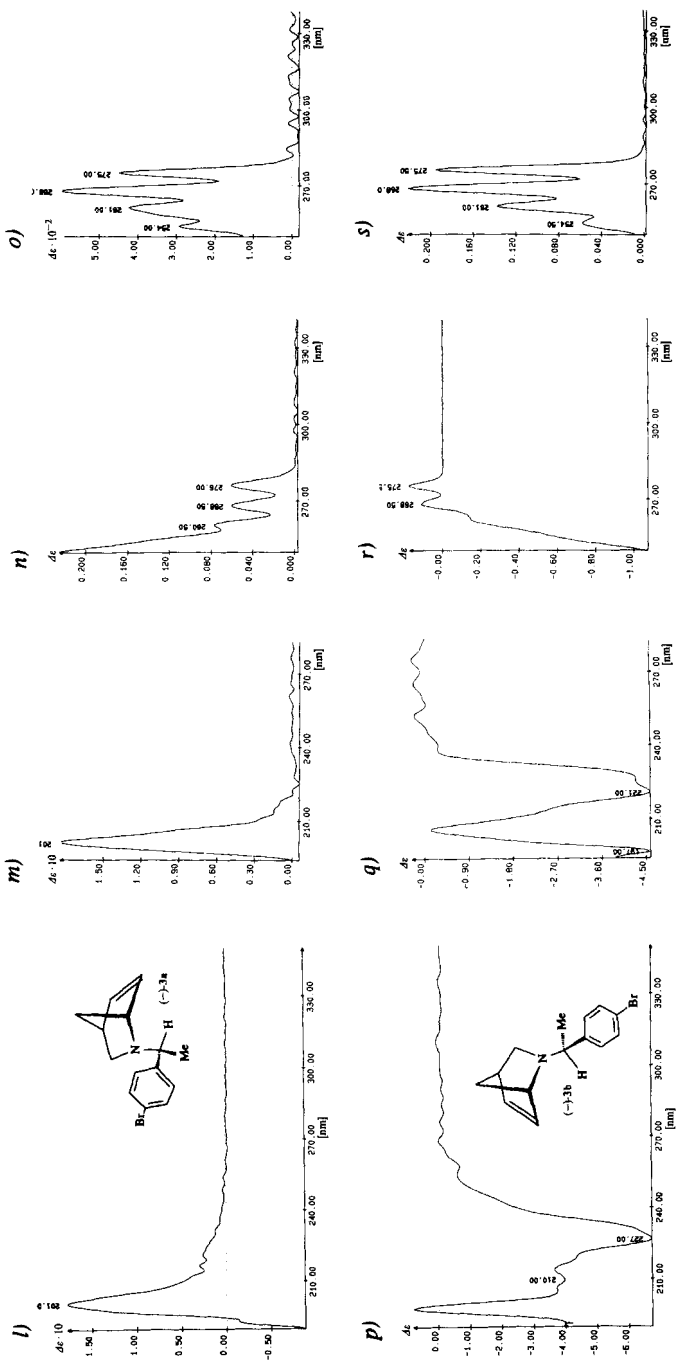


Fig. 3. *CD Spectra of the pairs of compounds* **1**–**3**. For details, see *Exper. Part.* (+)-**1**: *a*) MeOH, $l = 0.1$ mm; *b*) MeOH/HCl, $l = 0.1$ mm; *c*) MeOH/HCl, $l = 1.0$ mm. (−)-**2a**: *d*) MeOH, $l = 0.1$ mm; *e*) MeOH/HCl, $l = 0.1$ mm; *f*) MeOH, $l = 1.0$ mm; *g*) MeOH/HCl, $l = 1.0$ mm. (+)-**2b**: *h*) MeOH, $l = 0.1$ mm; *i*) MeOH/HCl, $l = 0.1$ mm; *j*) MeOH, $l = 1.0$ mm; *k*) MeOH/HCl, $l = 10.0$ mm. (−)-**3a**: *l*) MeOH, $l = 0.1$ mm; *m*) MeOH/HCl, $l = 0.1$ mm; *n*) MeOH, $l = 10.0$ mm; *o*) MeOH/HCl, $l = 10.0$ mm. (−)-**3b**: *p*) MeOH, $l = 0.1$ mm; *q*) MeOH/HCl, $l = 0.1$ mm; *r*) MeOH, $l = 10.0$ mm; *s*) MeOH/HCl, $l = 10.0$ mm.

workers extensively explored the relative importance of *exo*-transition states and diastereofacial selectivities in *Diels-Alder* reactions in aqueous solvents [14]. Solvent effects were also shown to be important in aza-*Diels-Alder* reactions [4]. In the case of (–)-(*S*)-1-(4-bromophenyl)ethylamine, reaction in DMF resulted in a 2.4:1 *ul*/*lk* ratio, albeit the combined isolated yield of (–)-**3a**/(–)-**3b** was lower (65%) than from the reaction in H_2O, and some unidentified decomposition products were formed. We took as end-point of the reaction the disappearance of starting amine. Further studies are necessary to clarify the time course, kinetic parameters, and the role of solvent polarity in this reaction.

CD Spectra. The CD spectra of the enantiomer (+)-**1** and of the diastereoisomers (–)-**2a**/(+)-**2b** and (–)-**3a**/(–)-**3b** were determined in both MeOH and MeOH/HCl (*Fig. 3*; for full data and corresponding UV spectra, see *Exper. Part*).

The enantiomers (+)- and (–)-**1** were separated by repeated HPLC on a *Chiracel-ODS* column, as described elsewhere [15]. The UV absorption spectra in MeOH of (+)-**1** shows a maximum at 191 mm ($\varepsilon = 32300$), a shoulder at *ca.* 205 nm ($\varepsilon = 11800$), and a gradually increasing absorbance with diminishing wavelength, with small shoulders at 257 ($\varepsilon = 366$) and 263 nm ($\varepsilon = 230$). Protonation (MeOH/HCl) results in a bathochromic shift of an overlapping band and allows the observation of the weak ^1L_b band between 250 and 270 nm, with λ_{max} 268 ($\varepsilon = 183$), 262 ($\varepsilon = 249$), and 257 ($\varepsilon = 246$), whereas the shoulder at 205 nm decreases slightly in intensity ($\varepsilon = 10200$).

The CD spectrum of (+)-**1** in MeOH (*Fig. 3a*) shows a large positive maximum at 195 nm ($\Delta\varepsilon = 15.4$). In MeOH/HCl (*Fig. 3b*), this maximum is enhanced in intensity (λ_{max} 196.5 nm; $\Delta\varepsilon = 21.7$), and a shoulder at 205–220 nm ($\Delta\varepsilon_{205} = ca.\ 8$) can be clearly observed. Additionally, the protonated (+)-**1** shows a weak *Cotton* effect at 257 nm ($\Delta\varepsilon = +0.017$; *Fig. 3c*), which cannot be seen in neutral solution. Protonation does not change the sign of the observed *Cotton* effects, which is indicative that, in this case, both the protonated and the neutral species exist in analogous conformations.

In the longer-wavelength range, chiral olefins give rise to CD bands in the region 190–200 nm assigned to $\pi \rightarrow \pi^*$ transitions and in the region of 210–230 nm corresponding to *Rydberg* transitions ($\pi \rightarrow 3s$, $A_{1g} \rightarrow B_{3u}$) [17]. The benzyl chromophore, on the other hand, can present *Cotton* effects around 250–270 nm corresponding to the ^1L_b band (B_{2u}) and around 210 nm ($\pi \rightarrow \pi^*$) [18]. The interaction between the ($\pi \rightarrow \pi^*$) transitions of the aromatic and the olefinic chromophores gives rise to exciton coupling phenomena and was employed in the determination of absolute configurations in benzoates derived from allylic alcohols [16].

The highest frequency absorption, due to the $B_{2u}(^1L_b)$ transition, was thoroughly studied in systems containing a chiral benzylic centre, and attempts were made to formulate chirality rules for the benzene chromophore based on this transition [18]. For the B_{2u} transition to be observable, the benzyl moiety must be prevented from freely rotating among the single bond which connects it to the chiral portion of the molecule [19]. The foregoing ^{1}H-NMR studies established that in $CDCl_3$ the azabicycloheptanes **2**–**4** adopt a strongly preferred conformation. As can be demonstrated by the observation of the B_{2u} transition (*Fig. 3c*), this is also the case for (+)-**1** in acidic MeOH. There is, however, insufficient precedent to enable an unambiguous assignment of the configuration of the enantiomers of **1** from this transition alone, in the absence of additional evidence.

For the case of exciton coupling among two symmetrical chromophores, two *Cotton* effects are expected, with opposing signs. The sign of the *Cotton* effect observed at the longer wavelength corresponds to the helicity relationship between the corresponding chromophores. In the case of benzoates derived from allylic alcohols, due to a strong band below 200 nm, two bands of similar sign are observed, and the helicity of the system corresponds to the sign of the longer-wavelength band [16]. The benzyl and olefin chromophores are expected to present analogous exciton-coupling effects. Thus, the positive shoulder at *ca.* 200 nm implies a positive chirality relationship (helicity) among the chromophores of (+)-**1**, whereas the opposite is the case for the negative chirality relationship in (−)-**1** as shown in *Fig. 4*. If the preferred conformation of (+)-**1** in solution is that with the benzyl moiety in the *endo*-face of the ring, the absolute configuration of (+)-**1** is 1*R*. This conclusion can be further probed by reference to the CD spectra of the diastereoisomer pairs (−)-**2a**/(+)-**2b**, and (−)-**3a**/(−)-**3b**, of known configuration.

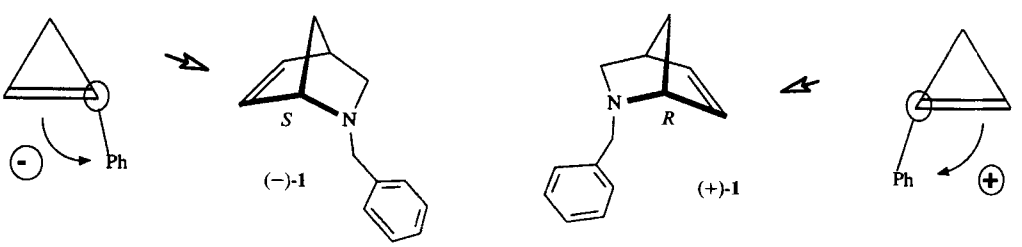


Fig. 4. *Positive exciton chirality relationship of the olefin and the phenyl chromophores of (+)-***1** *(1*R*) corresponding to a positive sign of the* Cotton *effect at 200–220 nm* (the converse is the case for (−)-**1**)

As for (+)-**1**, the ^1L_b transition is clearly seen in the case of (−)-**2a**, (+)-**2b**, (−)-**3a**, and (−)-**3b** in MeOH/HCl (*Figs. 3g, 3k, 3o,* and *3s*), although it can already be detected in MeOH, at appropriate concentration and path length (*Figs. 3f, 3j, 3n,* and *3r*). It is to be noted that acidifying of the solvent does not modify the sign of the longer-wavelength *Cotton* effects, indicating, as for (+)-**1**, that the preferred conformations in both cases are not altered by protonation. However, the CD spectra of the diastereoisomer pairs **2** and **3** are further complicated by the presence of the additional chiral benzylic centre. Benzylic substitution, however, mainly affects the longer-wavelength ^1L_b transition. Thus, the spectra can be interpreted in terms of two overlapping phenomena: *a*) the interacting $\pi \rightarrow \pi^*$ transitions of the olefin and the aromatic nucleus, giving rise to bands due to exciton coupling in the 200–230 nm range, and *b*) the bands due to vibronic coupling of the benzylamine with the aromatic nucleus, corresponding to the ^1L_b transition, in the 250–280-nm range. The latter transition is expected to be similar in both diastereoisomers arising from the same chiral amine, whereas the former band constitutes the distinguishing factor among diastereoisomers. This is clearly the case for the diastereoisomer pairs (−)-**2a**/(+)-**2b** and (−)-**3a**/(−)-**3b**. The weak absorptions corresponding to the ^1L_b band are negative for both (−)-**2a** and (+)-**2b** (*Figs. 3g* and *3k*, resp.), as they share the (1′*R*)-configuration from (*R*)-1-phenylethylamine ([20]: CD: 268 nm ($\Delta\varepsilon = -0.11$)). Correspondingly both (−)-**3a** and (−)-**3b** have positive *Cotton* effects in the 250–270-nm

region[2]), which accords with their sharing the opposite chirality of the benzylamine with respect to (−)-**2a** and (+)-**2b**. However, the diastereoisomer pairs present opposite effects in the 195–230-nm region. Thus, diastereoisomers with (1*R*)-configuration, *i.e.* (+)-**2b** and (−)-**3a** have positive *Cotton* effects in this region, whereas the converse is found for (−)-**2a** and (−)-**3b**, both with the (1*S*)-configuration. Thus, the assignment of (1*R*)-configuration to (+)-**1** is further justified on empirical grounds.

In electronic absorption spectra, the ^1L_a band of nitrobenzene is observed at *ca.* 268 nm, but the ^1L_b band is presumably obscured by overlapping absorptions [22]. For diastereoisomers (+)-**4a** and (−)-**4b**, the CD spectra are of further complexity, presumably due to overlapping transitions arising from the NO_2 group.

Conclusion. – 2D-COSY/ROESY Experiments provide a convenient and reliable methodology for the study of conformational preferences and the assignment of relative configurations in systems of small molecular weight such as those studied here. This may now be applied in conjunction with CD spectroscopy to assign the absolute configurations in other similar systems.

Novel chiral amines and reaction conditions in the aza-*Diels-Alder* reaction may further enhance the stereoselectivity. For preparative purposes, due to the low cost of both enantiomers of 1-phenylethylamine, and the relative ease of separation of the diastereoisomeric adducts, we resigned ourselves to the modest diastereoselectivity [5] [6]. Other laboratories have recently demonstrated the possibility of inducing high stereoselectivity in analogous aza-*Diels-Alder* reactions using a chiral catalyst [2b]. Improved methods for the obtention of these compounds will increase the already great versatility of these azabicyclic systems as starting materials in stereospecific synthesis.

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Experimental Part

General. Solvents and (+)-(*R*)-α-methyl-4-nitrobenzylamine hydrochloride were purchased from *Merck*, (−)-(*S*)-1-(4-bromophenyl)ethylamine from *Schweizerhall*, and the other reagents from *Fluka*. TLC: *Merck* silica gel *60* F_{254} anal. plates; detection by UV or spraying with I_2 soln. I_2 (25 g), KI (20 g), EtOH/H_2O 1:4 (1000 ml). M.p.: *Büchi-510* melting-point apparatus; in open capillaries; uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter; 1-ml microcuvette (l = 10 cm). UV/VIS: (λ_{max} [nm] (ε)): *Lambda 9*. CD (λ_{max} [nm] ($\Delta\varepsilon$ [$dm^3mol^{-1}cm^{-1}$])): *Jobin Yvon CD-6*; solvent cutoff defined for reference solvent absorbance = 2. IR ($\tilde{\nu}$ [cm^{-1}]): *Bruker IFS 66 FT-IR*. ^{1}H- and ^{13}C-NMR (δ in ppm, J in Hz): *Bruker AM 500* (^{1}H, 500 MHz), *Bruker AMX 400* (^{1}H, 400 MHz; ^{13}C, 100.62 MHz), *Bruker AM 360* (^{1}H, 360 MHz; ^{13}C, 90.6 MHz); protons were fully assigned by homonuclear 2D-shift correlation with double-quantum filter (COSY), using the modified-phase cycle by *Derome* and *Williamson* [23], C-atoms were fully assigned from J-modulated spin-echo ^{13}C spectra, followed by 2D ^{1}H,^{13}C correlation *via* heteronuclear zero- and double-quantum coherence with low-pass filter to suppress one-bond correlations, with no decoupling during acquisition [24], and 2D ^{1}H,^{13}C correlation *via* heteronuclear zero- and double-quantum coherence, using the phase-sensitive BIRD sequence with decoupling during acquisition [25]. MS (m/z (%)): *VG TS 250* (EI, 70 eV); *Varian MAT 212* (FAB, 8 keV).

(+)-(1R)-2-(Phenylmethyl)-2-azabicyclo[2.2.1]hept-5-ene ((+)-**1**). Colourless oil. $[\alpha]_D^{20}$ = +53.5 (c = 0.23, CH_2Cl_2). UV (c = 2.618, MeOH, l = 1.0 mm); 257 (sh, 352), 263 (sh, 237). UV (c = 2.618, MeOH/HCl, l = 1.0

[2]) This behaviour is, however, the *opposite* of what is reported for (−)-(*S*)-1-(4-bromophenyl)ethylamine [21]: CD: 277 ($\Delta\varepsilon$ = −0.05), 270 ($\Delta\varepsilon$ = −0.05), 263 ($\Delta\varepsilon$ = −0.02).

mm): 286 (181), 262 (256), 257 (257). UV (c = 1.173, MeOH, l = 0.1 mm): 205 (sh, 11800), 191 (32300). CD (c = 3.492 mM, MeOH, l = 0.1 mm): 196.5 (+15.4). CD (c = 3.492 mM, MeOH/HCl, l = 0.1 mm): 195.5 (+21.7), 205 (sh, +9). CD (c = 34.92 mM, MeOH, l = 1.0 mm): 257.5 (+0.017).

(+)-(1R,1'S)- and (−)-(1S,1'S)-2-(1'-Phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene ((+)-**2a** and (−)-**2b**, resp.). Formaldehyde (37%; 31.15 ml, 0.39 mol) was added to a soln. of (−)-(*S*)-1-phenylethylamine hydrochloride (43 g, 0.27 mol) in H_2O (120 ml) and the soln. stirred at 0° for 15 min. Then freshly distilled cyclopentadiene (50 ml, 0.76 mol) was added. The mixture was vigorously stirred at 0° for 4 h and then diluted with H_2O (500 ml) and washed (hexane/Et_2O 1:1, 3 × 200 ml). The aq. layer was made alkaline by addition of KOH pellets and extracted with Et_2O (3 × 200 ml). The org. extracts were dried (Na_2SO_4) and evaporated. The crude product was chromatographed (silica gel, *t*-BuOMe/MeOH/NH_4OH 97:3:0.3): (+)-**2a** (26.7 g, 50%; R_f 0.5) and (−)-**2b** (6.5 g, 12%; R_f 0.4) as colourless oils.

(+)-**2a**: $[\alpha]_D^{20}$ = +21 (c = 0.8, CH_2Cl_2). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.34 (*dd*, J = 9.0, 1.5, H_{endo}–C(3)); 1.36 (*d*, J = 6.0, 3 H–C(2')); 1.45 (*dq*, J = 8.6, 2.3, 1 H, H–C(7)); 1.58 (*dt*, J = 8.6, 2.3, 1 H, H–C(7)); 2.81 (*m*, H–C(4)); 2.90 (*dd*, J = 9.0, 3.0, H_{exo}–C(3)); 3.05 (*q*, J = 6.0, H–C(1')); 4.14 (*m*, H–C(1)); 6.10 (*dd*, J = 6.0, 2.8, H–C(6)); 6.31 (*ddd*, J = 6.0, 3.2, 1.5, H–C(5)); 7.15–7.34 (*m*, 5 arom. H). ^{13}C-NMR (100.62 MHz, $CDCl_3$): 23.54 (C(2')); 43.51 (C(1)); 47.70 (C(7)); 52.50 (C(3)); 62.07 (C(4)); 63.49 (C(1')); 126.51 (C(4'')); 127.36 (C(2''), C(6'')); 128.07 (C(3''), C(5'')); 130.14 (C(6)); 136.23 (C(5)); 146.6 (C(1'')). EI-MS: 199 (14, M^+), 184 (10), 105 (100).

(−)-**2b**: $[\alpha]_D^{20}$ = −140 (c = 1.0, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.28 (*dd*, J = 9.0, 2.5, H_{endo}–C(3)); 1.30 (*d*, J = 6.2, H–C(2')); 1.55 (*d*, J = 7.5, 1 H, H–C(7)); 1.67 (*dd*, J = 7.5, 1.5, 1 H, H–C(7)); 2.92 (*m*, H–C(4)); 2.93 (*q*, J = 6.0, H–C(1')); 3.30 (*dd*, J = 9.0, 3.0, H_{exo}–C(3)); 3.50 (*m*, H–C(1)); 5.83 (*dd*, J = 5.8, 2.5, H–C(6)); 6.32 (*ddd*, J = 5.8, 4.0, 1.5, H–C(5)); 7.28–7.35 (*m*, 5 arom. H). ^{13}C-NMR (100.62 MHz, $CDCl_3$): 23.72 (C(2')); 43.92 (C(4)); 47.67 (C(7)); 51.72 (C(3)); 62.97 (C(1)); 63.79 (C(1')); 126.87 (C(4'')); 127.52 (C(2''), C(6'')); 128.29 (C(3''), C(5'')); 130.65 (C(6)); 135.78 (C(5)); 145.45 (C(1'')). EI-MS: 199 (15, M^+), 184 (13), 105 (100).

The corresponding enantiomers (−)-**2a** (1*S*,1'*R*) and (+)-**2b** (1*R*,1'*R*) were obtained as colourless oils in analogous fashion from (+)-(*R*)-1-phenylethylamine.

(−)-**2a**: $[\alpha]_D^{20}$ = −23 (c = 4.5, CH_2Cl_2). UV (c = 0.864, MeOH, l = 1.0 mm): 257 (sh, 366), 263 (sh, 230). UV (c = 0.864, MeOH/HCl, l = 1.0 mm): 251 (226), 257 (250), 262 (208). UV (c = 0.864, MeOH, l = 0.1 mm): 205 (sh, 11800). UV (c = 0.864, MeOH/HCl, l = 0.1 mm): 205 (sh, 10200). CD (c = 4.335 mM, MeOH, l = 1.0 mm): 254 (−0.308), 261 (−3.04), 268 (−0.21). CD (c = 4.335 mM, MeOH/HCl, l = 1.0 mm): 254 (−0.06), 261 (−0.09), 268 (−0.08). CD (c = 4.335 mM, MeOH, l = 0.1 mm): 195.5 (−28.2). CD (c = 4.335 mM, MeOH/HCl, l = 0.1 mm): 196 (−23.2), 216 (+1.28).

(+)-**2b**: $[\alpha]_D^{20}$ = +146.4 (c = 4.7, CH_2Cl_2). UV (c = 0.868, MeOH, l = 1.0 mm): 257 (sh, 292), 263 (sh, 199). UV (c = 0.868, MeOH/HCl, l = 1.0 mm): 251 (225), 257 (267), 261 (244), 267 (168). UV (c = 0.868, MeOH, l = 0.1 mm): 205 (sh, 13000). UV (c = 0.868, MeOH/HCl, l = 0.1 mm): 205 (sh, 10900). CD (c = 4.355 mM, MeOH, l = 1.0 mm): 222.5 (+4.32). CD (c = 4.355 mM, MeOH/HCl, l = 10.0 mm): 254 (−0.0053), 261 (−0.0302), 268 (−0.02). CD (c = 4.355 mM, MeOH, l = 0.1 mm): 195.5–230 (br., *ca.* 4). CD (c = 4.335 mM, MeOH/HCl, l = 0.1 mm): 198 (+6.26), 214 (+6.73).

(−)-(1R,1'S)- and (−)-(1S,1'S)-2-[1'-(4''-Bromophenyl)ethyl]-2-azabicyclo[2.2.1]hept-5-ene ((−)-**3a** and (−)-**3b**, resp.). As described for (+)-**2a**/**2b**. Ratio (−)-**3a**/(−)-**3b** 1.4:1.

(−)-**3a**: Colourless crystals. M.p. *ca.* 35°. R_f (silica gel, *t*-BuOMe/MeOH/NH_4OH 95:5:0.5) 0.62. $[\alpha]_D^{20}$ = −8.96 (c = 2.9, CH_2Cl_2). UV(c = 0.610, MeOH/HCl, l = 10.0 mm): 258 (sh, 344), 264 (sh, 328). UV (c = 0.870, MeOH, l = 0.1 mm): 194 (49700), 219 (11800). UV (c = 0.870, MeOH/HCl, l = 0.1 mm): 196 (46100), 225 (11500). CD (c = 2.192 mM, MeOH, l = 10.0 mm): 260.5 (+0.077), 268.5 (+0.06), 276 (+0.06). CD (c = 2.192 mM, MeOH/HCl, l = 10.0 mm): 254 (+0.0294), 261 (+0.042), 268 (+0.060), 275 (+0.040). CD (c = 3.127 mM, MeOH, l = 0.1 mm): 201 (+17.7). CD (c = 3.127 mM, MeOH/HCl, l = 0.1 mm): 201 (+18.4). IR (KBr): 529, 721, 736, 822, 908, 1010, 1068, 1095, 1214, 1332, 1403, 1484, 2859, 2943, 2794. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.26 (*dd*, J = 8.72, 1.68, H_{endo}–C(3)); 1.30 (*d*, J = 6.52, 3 H–C(2')); 1.45 (*dd*, J = 8.0, 1.6, 1 H, H–C(7)); 1.59 (*d*, J = 7.92, 1 H, H–C(7)); 2.83 (*s*, H–C(4)); 2.87 (*dd*, J = 8.8, 3.08, H_{exo}–C(3)); 3.00 (*q*, J = 6.52, H–C(1')); 4.11 (br. *s*, H–C(1)); 6.09 (*dd*, J = 5.68, 1.72, H–C(6)); 6.31 (*m*, H–C(5)); 7.21 (*d*, J = 6.6, H–C(2''), H–C(6'')); 7.38 (*d*, J = 6.6, H–C(3''), H–C(5'')). ^{13}C-NMR (100.62 MHz, $CDCl_3$): 23.47 (*Me*–C(1')); 43.52 (C(4)); 47.72 (C(7)); 52.54 (C(3)); 62.05 (C(1)); 62.95 (C(1')); 120.07 (C(4'')); 129.11 (C(2''), C(6'')); 130.01 (C(6)); 131.19 (C(3''), C(5'')); 136.35 (C(5)); 145.2 (C(1'')). FAB-MS (thioglycerol): 280 (90), 278 (100, MH^+), 214 (43), 212 (42), 185 (44), 183 (58). Anal. calc. for $C_{14}H_{16}NBr$: C 60.5, H 5.8, N 5.0; found: C 59.8, H 5.7, N 5.0.

(−)-**3b**: Colourless crystals. M.p. 48–49°, R_f (silica gel, *t*-BuOMe/MeOH/NH_4OH 95:5:0.5) 0.48. $[\alpha]_D^{20}$ = −152.8 (c = 2.8, CH_2Cl_2). UV (c = 0.714, MeOH, l = 10.0 mm): 265 (322). UV (c = 0.714, MeOH/HCl, l = 10.0 mm): 259 (265), 265 (277). UV (c = 0.714, MeOH, l = 0.1 mm): 195 (48900), 219 (12550). UV (c = 0.714,

MeOH/HCl, l = 0.1 mm): 197 (46500), 225 (11900). CD (c = 2.566 mM, MeOH, l = 10.0 mm): 268.5 (+0.10), 275.5 (0.17). CD (c = 2.566 mM, MeOH/HCl, l = 10.0 mm): 254.5 (+0.06), 261 (+0.14), 268 (+0.22), 275 (+0.20). CD (c = 2.566 mM, MeOH, l = 0.1 mm): 210 (−3.95), 227 (−7.72). CD (c = 2.566 mM, MeOH/HCl, l = 0.1 mm): 197 (−4.54), 221 (−4.59). IR (KBr): 553, 717,725, 825, 843, 1013, 1089, 1095, 1186, 1292, 1303, 1484, 2965, 2976. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.24 (*d*, J = 6.4, 3 H–C(2′)); 1.27 (*d*, J = 8.12, 1 H, H–C(7)); 1.54 (*d*, J = 8.12, 1 H, H–C(7)); 1.64 (*dd*, J = 8.6, 1.5, H_{endo}–C(3)); 2.93 (*q*, J = 6.4, H–C(1′)); 2.93 (*s*, overlapping, H–C(4)); 3.46 (*s*, H–C(1)); 5.80 (*dd*, J = 5.64, 1.68, H–C(6)); 6.31 (*m*, H–C(5)); 7.21 (*d*, J = 8.3, H–C(2″), H–C(6″)); 7.45 (*d*, J = 8.3, H–C(3″), H–C(5″)). ^{13}C-NMR (100.62 MHz, $CDCl_3$): 23.66 (*Me*–C(1′)); 43.90 (C(4)); 47.72 (C(7)); 51.59 (C(3)); 62.97 (C(1)); 63.11 (C(1′)); 120.50 (C(4″)); 129.27 (C(2″), C(6″)); 130.43 (C(6)); 131.46 (C(3″), (C(5″)); 136.19 (C(5)); 144.55 (C(1″)). FAB-MS (thioglycerol): 280 (100), 278 (98, MH$^+$), 185 (40), 183 (45). Anal. calc. for $C_{14}H_{16}NBr$: C 60.5, H 5.8, N 5.0; found: C 60.2, H 5.9, N 5.0.

(+)-(1S,1′R)- and (−)-(1R,1′R)-2-[1′-(4″-Nitrophenyl)ethyl]-2-azabicyclo[2.2.1]hept-5-ene ((+)-**4a** and (−)-**4b**, resp.). As described for (−)-**2a**/(+)-**2b**. Ratio (+)-**4a**/(−)**4b** 1.2:1.

(+)-**4a**: Light yellow crystals. M.p. 86–88°. R_f (silica gel, *t*-BuOMe/MeOH/NH_4OH 95:5:0.5) 0.76. $[\alpha]_D^{20}$ = +23.5 (c = 0.23, CH_2Cl_2). CD (c = 3.424 mM, MeOH, l = 0.10 mm): 195.5 (+9.3), 205 (+1.15), 223 (+4.35), 267 (−1.59), 309.5 (+0.71). IR (KBr): 1340, 1351, 1519, 1596. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.21 (*dd*, J = 8.64, 1.72, H_{endo}–C(3)); 1.34 (*dd*, J = 8.64, 1.72, 3 H–C(2′)); 1.48 (*dd*, J = 8.12, 1.68, 1 H, H–C(7)); 1.60 (*d*, J = 8.12, 1 H, H–C(7)); 2.86 (br. *s*, H–C(4)); 2.90 (*dd*, J = 8.64, 3.12, H_{exo}–C(3)); 3.15 (*q*, J = 6.56, H–C(1′)); 4.14 (*d*, J = 1.44, H–C(1)); 6.11 (*dd*, J = 5.76, 1.92, H–C(6)); 6.33 (*m*, H–C(5)); 7.51 (*d*, J = 8.5, H–C(2″), H–C(6″)); 8.14 (*d*, J = 8.5, H–C(3″), H–C(5″)). ^{13}C-NMR (100.62 MHz, $CDCl_3$): 23.25 (Me–C(1′)); 43.50 (C(4)); 47.53 (C(3)); 52.64 (C(7)); 62.01 (C(1)); 63.14 (C(1′)); 123.46 (C(3″), C(5″)); 128.04 (C(2″), C(6″)); 129.83 (C(6)); 136.44 (C(5)); 146.76 (C(1″)); 154.30 (C(4″)). FAB-MS (thioglycerol): 245 (49, MH$^+$), 179 (100), 150 (40).

(−)-**4b**: Light yellow crystals. M.p. 50–53°. R_f (silica gel, *t*-BuOMe/MeOH/NH_4OH 95:5:0.5) 0.63. $[\alpha]_D^{20}$ = −143.2 (c = 0.25, CH_2Cl_2). CD (c = 3.88 mM, MeOH, l = 0.10 mm): 196.5 (+1.94), 210 (−1.74), 238 (−2.33), 260 (−3.15), 317 (+0.4). IR (KBr): 1350, 1519, 1606. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (*d*, J = 6.2, 3 H–C(2′)); 1.29 (overlapping *m*, 1 H, H–C(7)); 1.55 (*d*, J = 7.6, 1 H, H–C(7)); 1.68 (*d*, J = 8.52, H_{endo}–C(3)); 2.94 (*s*, H–C(4)); 3.10 (*q*, J = 6.2, H–C(1′)); 3.27 (*d*, J = 7.2, H_{exo}–C(3)); 3.41 (*s*, H–C(1)); 5.79 (*d*, J = 5.08, H–C(6)); 6.35 (br. *s*, H–C(5)); 7.50 (*d*, J = 8.12, H–C(2″), H–C(6″)); 8.18 (*d*, J = 8.12, H–C(3″), H–C(5″)). ^{13}C-NMR (100.62 MHz, $CDCl_3$): 23.58 (*Me*–C(1′)); 43.73 (C(4)); 47.75 (C(7)); 51.14 (C(3)); 62.91 (C(1)); 62.95 (C(1′)); 123.64 (C(3″), C–(5″)); 128.20 (C(2″), C(6″)); 130.02 (C(6)); 136.70 (C(5)); 146.93 (C(1″)); 153.28 (C(4″)). FAB-MS (thioglycerol): 245 (53, MH$^+$), 179 (100).

(−)-(1R,2R,3R,4R,6R,1′S)-3-Bromo-1-(1′-phenylethyl)-1-azoniatricyclo[2.2.1.0^{2,6}]heptyl Bromide ((−)-**5**). A soln. of (+)-**2a** (15 g, 75 mmol) in CH_2Cl_2 (50 ml) was added dropwise over 1 h to a soln. of Br_2 (3.5 ml. 67 mmol) in CH_2Cl_2 (25 ml), and the resulting mixture was kept at 4° during 16 h. The yellow crystals which formed were filtered and recrystallised from CH_2Cl_2/Et_2O: 19.7 g (73%) of colourless crystals. M.p. 196–198°. $[\alpha]_D^{20}$ = −6.0 (c = 1.1, CH_2Cl_2). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.89 (*d*, J = 6.0, 3 H–C(2′)); 2.50 (*s*, 2 H–C(7)); 2.90 (*s*, H–C(4)); 3.48 (*d*, J = 8.0, 1 H, H–C(5)); 3.55 (*d*, J = 8.0, 1 H, H–C(5)); 4.40–4.60 (*m*, H–C(6), H–C(2), H–C(3)); 5.81 (*m*, H–C(1′)); 7.40–7.72 (*m*, 5 arom. H). FAB-MS (thioglycerine): 280 (97), 278 (100 M^+). Anal. calc. for $C_{14}H_{17}NBr_2$: C 46.8, H 4.8, N 3.9, Br 44.5; found: C 46.8, H 4.6, N 4.0, Br 44.3.

Crystal-Structure Determination of (−)-**5**. The compound was crystallised from CH_2Cl_2/Et_2O to give colourless crystals. Crystal data: $C_{14}H_{17}NBr_2$, M 359.1; space group $P4_1$; $a = b$ = 6.447(3), c = 34.722(9) Å; V = 1442.2 Å^3; d_{calc} = 1.653 g/cm^3; Z = 4; μ = 70.16 cm^{-1}; crystal dimensions 0.45 × 0.40 × 0.25 mm. Intensities were measured on an *Enraf-Nonius-CAD-4* diffractometer, using monochromated CuK_α radiation to Θ < 60°; counting time 70 s. Maximum decay correction factors were in the range 0.957 to 1.045. Empirical absorption correction factors from 0.88 to 1.12 based on a 360° Θ scan. Of the measured 2144 reflections, 2039 had $I > 2.5\,\sigma(I)$ and were considered observed. The structure was solved by direct methods, using SHELX-86 [26] and refined using SHELX-76 [27]. All H-atoms were included in idealised calculated positions. The final R factor was 0.041. The absolute configuration was determined using anomalous dispersion. The R factor using all data for $P4_1$ is 0.0410 compared to R = 0.0471 for the enantiomeric structure in $P4_3$. Using a selected set of 50 reflections showing the strongest anomalous effect [10], the discrimination between $P4_1$ and $P4_3$ was more pronounced, with an R factor of 0.0339 for $P4_1$ compared to an R factor of 0.0578 for $P4_3$. Fractional atomic coordinates and anisotropic temperature factors of the non-H-atoms were deposited with and are available on request from the director of the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, England.

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