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Stereochemical outcome of the T-reaction employing chiral bicyclic amines

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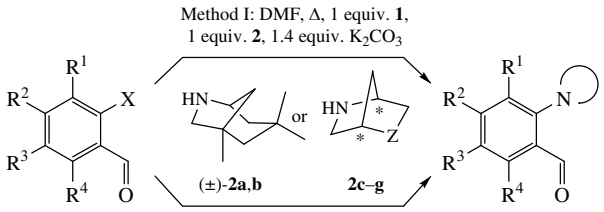
Using the T-reaction as a tandem-style condensation–cyclization and ring closure *via* the *tert*-amino effect as a key step, we prepared new chiral heterocyclic systems and rationalised the regio- and stereoselectivity of the products.

It is well known[1–3] that cyclization *via* the *tert*-amino effect is attractive for preparing pharmacologically interesting fused tetrahydroquinolines in excellent yields and purity.[4] The mechanism of this isomerization has been thoroughly investigated.[5,6] We sought to explore the outcome of this reaction employing bicyclic amines.

ortho-Aminobenzaldehyde intermediates **3** (Scheme 1, Table 1) were prepared by the reaction of bicyclic secondary amines[7] **2** with substituted 2-halobenzaldehydes *via* either nucleophilic aromatic substitution of 2-fluorobenzaldehyde using K_2CO_3 in DMF[5] (method I), or Buchwald–Hartwig-type Pd-catalysed aryl amination of 2-bromobenzaldehyde[8,9] (method II).†

Thermal isomerization/cyclization by the *tert*-amino effect can be carried out *via* either a stepwise condensation/cyclization procedure (method III) or as a tandem reaction[11] of Knövenagel condensation using 2,2-dimethyl-[1,3]dioxane-4,6-dione or 1,3-dimethylpyrimidine-2,4,6-trione (Scheme 2), followed by the ring closure of benzylidenic intermediates **4c**, respectively, in refluxing Bu^{n}OH (method IV). Taking into account the high inclination towards cyclization of the intermediate *ortho-tert*-amino-(α,α)-disubstituted styrenes,[4,12,13] the one-pot reaction was found preferable. The crude mixture of cyclised isomers was separated by MPLC on silica.



1 **3**

	N	R^1	R^2	R^3	R^4	Z	Configuration
3a	a	H	H	H	F	–	(±)
3b	b	H	F	H	H	–	(±)
3c	c	H	H	H	H	N–Bn	(*S*,*S*)
3d	d	H	H	H	H	N–4-FC_6H_4	(*S*,*S*)
3e	e	H	H	H	H	N–Boc	(*S*,*S*)
3f	f	F	F	F	F	N–Boc	(*S*,*S*)
3g	g	H	H	H	H	O	(*R*,*R*)

Scheme 1 Preparation of *ortho*-bicycloamino-substituted aldehydes **3**.

Verboom *et al.*,[5] and Nijhuis *et al.*,[6] have disclosed the operative mechanism in related thermal rearrangements of 2-vinyl-*N*,*N*-dialkylanilines into fused tetrahydroquinolines. The conversion was reasoned to proceed *via* an intramolecular [1,5]-hydride shift as the rate-determining step,[14] establishing a zwitterionic intermediate that subsequently undergoes cyclization. Most interestingly, although stereochemical information at the α-amino carbon from which the hydride migrates is temporarily lost, the transformation was demonstrated[6] to behave stereoselectively retaining the configuration of the original chiral centre, explained by a helically fixed intermediate.

Table 1 Preparation of *ortho*-bicycloalkylamino-substituted aldehydes **3** (see Scheme 1).

Product	Method	*T*/°C	*t*/h	Isolated yield (%)	Optical purity
3a	I	120	50	77	(±)
3b	I	120	80	71	(±)
3c	I	120	80	76	(*S*,*S*)
	II	95	20	75	
3d	I	110	100	61	(*S*,*S*)
3e	I	100	125	30	(*S*,*S*)
	II	95	18	70	
3f	I	110	100	75	(*S*,*S*)
3g	I	120	67	70	(*R*,*R*)

† **3c**: To a mixture of 1 equiv. of 2-fluorobenzaldehyde (708 mg, 5.71 mmol) in 30 ml of DMF, (1*S*,4*S*)-2-benzyl-2,5-diazabicyclo-[2.2.1]heptane, dihydrobromide (2000 mg, 5.71 mmol) and 3.4 equiv. of dry K_2CO_3 were added. The resulting mixture was heated under reflux for 80 h at 120 °C. The suspension was cooled to room temperature and poured into a half-saturated K_2CO_3 solution, extracted with CH_2Cl_2 (3×50 ml). The organic phases were combined and washed with 10 ml of brine; the brine was back extracted with 10 ml of CH_2Cl_2 and the combined organic phases were dried (Na_2SO_4). The solvent was rotoevaporated to yield the crude product, which was dissolved in CH_2Cl_2. An appropriate amount of 40-63 μm silica gel was added and the resultant mixture was concentrated on a rotary evaporator until no more solvent was distilled off. The adsorbed mixture was loaded into an MPLC cartridge for chromatographic separation, MPLC gradient PE to PE:EE = 80:20. Yield, 1209 mg (76%), amber oil, $[\alpha]_D^{20}$ +515.4 (*c* = 1.38, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.92 (s, 1H, CHO), 7.57 (dd, 1H, Ar-H^5, *J* 7.8 Hz, *J* 7.6 Hz), 7.25–7.06 (m, 6H, benzyl-Ar-H, H^3), 6.69 (br. d, 1H, Ar-H^4, *J* 7.4 Hz), 6.61 (d, 1H, Ar-H^6, *J* 8.4 Hz), 4.10 (br. s, 1H), 3.60 (dd, 1H, *J* 10 Hz, *J* 2.4 Hz), 3.51 (s, 2H), 3.38 (br. s, 1H), 2.95 (d, 1H, *J* 10 Hz), 2.84 (dd, 1H, *J* 9.8 Hz, *J* 1.8 Hz), 2.69 (d, 1H, *J* 9.8 Hz), 1.92–1.80 (m, 2H, bridge CH_2, *J* 9.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 190.0 (J), 149.2 (–), 139.3 (–), 134.1 (J), 128.4 (J), 127.9 (J), 126.6 (J), 123.9 (J), 123.6 (–), 117.1 (J), 115.7 (J), 62.4 (J), 61.5 (J), 58.5 (2J), 57.4 (2J), 57.2 (2J), 34.9 (2J). GC-MS, *m*/*z* [I_{rel} (%)]: 149.27 (100), 70.62 (83), 56.76 (78), 167.00 (51).

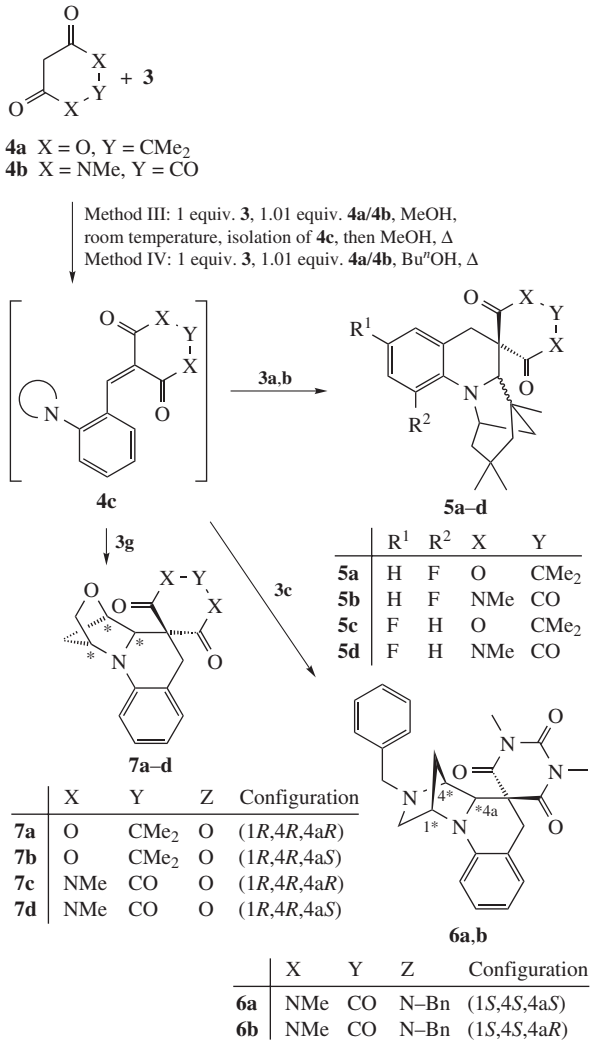
Table 2 Preparation of compounds **5–7** (see Scheme 2).

Product	Method	*T*/°C	*t*/h	Isolated yield (%)	Stereo-selectivity
5a			24	~100	
5b	IV	75	16	98	racemic
5c			30	85	
5d			20	~100	
6a,**b**	III	25	0.5	56	**6a**:**6b**, 7:1
		66	6	68	
	IV	75	30	93	**6a**:**6b**, 37:10
7a,**b**	IV	75	2	93	**7a**:**7b**, 2:11
7c,**d**	IV	100	6	83	**7c**:**7d**, 3:2

In a study on ring closure *via* the *tert*-amino effect, Nijhuis *et al*.[6] showed that cyclization takes place at the α-*tert*-amino carbon atom, which is better able to stabilise the iminium-type intermediate after a hydride shift. Therefore, three cyclised isomers **6a**, **6b**‡ and **8** (Schemes 2, 3) were envisioned.

Experimentally, we did not observe any compounds corresponding to structure type **8** (Scheme 3) where cyclization occurred on the more substituted carbon. This can be explained using Bredt's rule by the relatively high energy of an sp^2-hybridised carbon in a bridgehead position.

Thus, starting from homochiral **3c** and **3g** and being able to separate the resulting diastereomers of **6** and **7** we could deduce the absolute configuration at the new stereocentre *via*

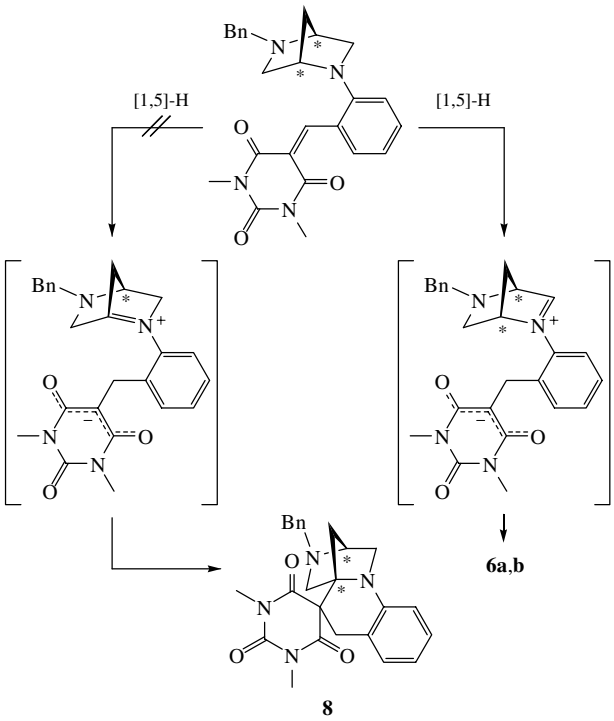


	R1	R2	X	Y
5a	H	F	O	CMe_2
5b	H	F	NMe	CO
5c	F	H	O	CMe_2
5d	F	H	NMe	CO

	X	Y	Z	Configuration
7a	O	CMe_2	O	(1*R*,4*R*,4a*R*)
7b	O	CMe_2	O	(1*R*,4*R*,4a*S*)
7c	NMe	CO	O	(1*R*,4*R*,4a*R*)
7d	NMe	CO	O	(1*R*,4*R*,4a*S*)

	X	Y	Z	Configuration
6a	NMe	CO	N–Bn	(1*S*,4*S*,4a*S*)
6b	NMe	CO	N–Bn	(1*S*,4*S*,4a*R*)

Scheme 2 Cyclocondensation–cyclization and ring closure *via* the *tert*-amino effect.



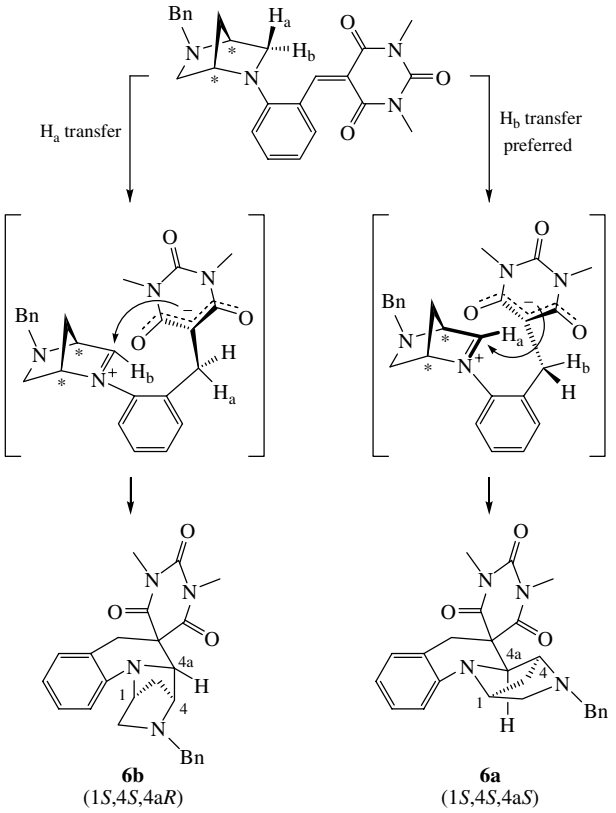
Scheme 3 Regioselectivity of cyclization *via* the *tert*-amino effect, compound **6**.

‡ **6a**, **6b**: Prepared from (1*S*,4*S*)-2-(5-benzyl-2,5-diazabicyclo[2.2.1]-hept-2-yl)benzaldehyde **3c** (272 mg, 1.93 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione **4b** (145 mg, 1.93 mmol). Bu^{n}OH, 5 ml, 100 h, 75 °C. MPLC gradient PE:CH_2Cl_2 = 88:12 to PE: CH_2Cl_2:Et_2O = 70:10:20. Yield of both isomers 375 mg (93%), slightly brown low-melting solid. **6a**:**6b** = 9.4:1, $[\alpha]_D^{20}$ +37.6 (*c* = 1.06, $CHCl_3$).

Alternatively: A solution of **3c** (6.89 mmol, 2 g) and **4b** (10.3 mmol, 1.61 g) in methanol (50 ml) was stirred for 40 h at room temperature. The solution was evaporated under reduced pressure and then purified by flash chromatography (100% EtOAc) to give an orange solid (31%). R_f (100% EtOAc) = 0.16. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.41 (s, 1H, C=CH), 7.73 (d, 1H, *J* 7.6 Hz), 7.35–7.26 (m, 6H), 6.81 (t, 2H, *J* 7.6 Hz), 3.27 (s, 3H, Me), 3.22 (s, 3H, Me). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.11, 162.5, 160.2, 156.5, 151.2, 149.7, 133.0, 132.4, 130.5, 130.1, 129.5, 128.9, 123.6, 119.6, 115.2, 114.9, 63.4, 61.1, 58.6, 56.2, 53.6, 34.8, 28.6, 28.0. The resulting product was dissolved in methanol, stirred under reflux for 6 h and further stirred overnight at room temperature. The mixture was evaporated under a reduced pressure and then purified by flash chromatography (8.5:1.5 to 6:4 PE:EE) to give a yellowish solid of **6a**:**6b** = 7:1 (68%).

6a: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.32 (m, 3H), 7.2–7.18 (m, 1H, Ar-H^9, *J* 7.6 Hz), 7.13 (br. d, 2 H, *J* 6.7 Hz), 7.01 (br. d, 1H, Ar-H^7, *J* 7.6 Hz), 6.68–6.65 (m, 1H, Ar-H^8, *J* 7.6 Hz), 6.65 (br. d, 1H, Ar-H^{10}, *J* 7.6 Hz), 4.43 (s, 1H, H^1), 4.05 (d, 1H, H^{4a}, *J* 2.4 Hz), 3.54 (d, 1H, N–CH_2-benzyl, *J* 12.6 Hz), 3.49 (d, 1H, N–CH_2-benzyl, *J* 12.6 Hz), 3.37 (br. s, 1H, H^4), 3.36 (d, 1H, H^6, *J* 16.1 Hz), 3.21 (s, 3H, NMe), 3.18 (s, 3H, NMe), 3.03 (d, 1H, H^2, *J* 9 Hz), 2.90 (d, 1H, H^6, *J* 16.1 Hz), 2.47 (d, 1H, H^2, *J* 9 Hz), 1.83 (s, 2H, H^{12}). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.3 (C$^{4'}$/C$^{6'}$), 164.4 (C$^{4'}$/C$^{6'}$), 150.7 (C$^{2'}$), 141.8 (C^{10a}), 137.6, 129.1, 128.6 (C^7), 128.3, 127.0, 126.8 (C^9), 119.0 (C^{6a}), 115.2 (C^8), 110.0 (C^9), 73.0 (C^1), 61.1 (C^2), 60.8 (C^{4a}), 59.5 (N–CH_2-phenyl), 57.6 (C^4), 44.3 (C^5), 38.5 (C^6), 33.3 (C^{12}), 28.4 (NMe), 28.1 (NMe).

6b: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.28 (m, 5H, benzyl-Ar-H), 7.18–7.15 (m, 1H, Ar-H^9, *J* 7.6 Hz), 7.13 (br. d, 1H, Ar-H^7, *J* 7.6 Hz), 6.73 (br. d, 1H, Ar-H^8, *J* 7.6 Hz), 6.65 (d, 1H, Ar-H^{10}, *J* 7.6 Hz), 4.37 (br. s, 1H, H^1), 3.83 (s, 1H, H^{4a}), 3.83 (d, 1H, N–CH_2-benzyl, *J* 13.4 Hz), 3.76 (d, 1H, H^6, *J* 16.6 Hz), 3.72 (d, 1H, N–CH_2-benzyl, *J* 13.4 Hz), 3.23 (br. s, 4H, NMe, H^{11}), 3.18 (m, 1H, H^2), 3.11 (s, 3H, NMe), 2.97 (d, 1H, H^6, *J* 13.4 Hz), 2.71 (d, 1H, H^2, *J* 9.1 Hz), 1.72 (d, 1H, H^{12}, *J* 9.5 Hz), 1.26 (d, 1H, H^{12}, *J* 9.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.6 (C$^{4'}$/C$^{6'}$), 168.3 (C$^{4'}$/C$^{6'}$), 151.4 (C$^{2'}$), 140.8 (C^{10a}), 139.3, 129.2 (C^7), 129.1, 128.9, 127.6, 127.3 (C^9), 119.4 (C^{6a}), 116.9 (C^8), 110.9 (C^4), 65.3 (C^1), 61.3 (C^{4a}), 59.5 (C^2), 59.2 (C^4), 56.6 (N–CH_2-phenyl), 49.3 (C^5), 34.3 (C^6), 33.9 (C^{12}), 29.2 (NMe), 28.9 (NMe).



6b (1*S*,4*S*,4a*R*) **6a** (1*S*,4*S*,4a*S*)

Scheme 4 Probable stereoselective mechanism of cyclization *via* the *tert*-amino effect.

the torsion angle H^4–C^4–C^{4a}–H^{4a} (Scheme 4) obtained from the vicinal coupling constant in 400 MHz ^{1}H NMR of protons H^4 and H^{4a} using the Karplus–Conroy relationship: in compounds **6a**, **7b** and **7d**, the signal corresponding to H^{4a} had a significantly lower vicinal coupling constant of $^3J_{H^{11},H^{13}} \leq 1.9$ Hz compared to isomers **6b**, **7a** and **7c**, indicating an almost orthogonal torsion angle and allowing to assign C^{4a} as (*S*) (Table 2). This observation and assignment was further supported by semi-empirical calculations at the MM+ and PM3 levels using geometry optimization in the HyperChem 8.0 molecular modeling software. Moreover, the assignments are in agreement with the values derived from HC- and HH-COSY NMR data.

Based on these findings, we conclude the following about the transformations of **3** to **6** and **7** (Scheme 2).

(1) In compounds **6** containing the (*S*,*S*)-diazabicyclo[2.2.1]-heptyl moiety, hydride migration of H_b located *trans* to the bridge took place preferentially resulting in the *S*-configuration of the newly formed stereocentre.

(2) Proceeding from the published suggestion[15] that a short distance between the α-amino hydrogen to the benzylidenic carbon in unsaturated intermediates **4c** (Scheme 2) might be a prerequisite for the [1,5]-hydride transfer and taking into account that compounds possessing a sterically demanding bridge CH_2 should attain a relative conformation placing the amino substituent at a maximum distance from the vinylic *ortho*-substituent (which can also be assumed to be directed away from the amino moiety[5,6]), we explain that the migration of hydrogen at the opposite face of the bridge CH_2 in the diazabicycloheptyl moiety is energetically favoured and thus **6a** is formed as the major product.

(3) Whether the observed stereochemical preference arises purely from steric repulsion of the bridge CH_2 with the vinylic carbanion in the dipolar intermediate, or at least partially from stereoelectronic effects establishing a shift preference through a selective rate acceleration of hydride migration, remains to be clarified. Contemplating the reverse ratio of stereoisomers seen with **7a** and **7b**, supported by HC- and HH-COSY-NMR, a full mechanistic elucidation may require consideration of both steric and stereoelectronic factors.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2007.11.005.

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