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Stereoselective intramolecular cycloadditions of homochiral nitrile imines: synthesis of enantiomerically pure 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-6(4*H*)-ones

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Abstract

Starting from the commercially available (*S*)-1-phenylethylamine, we have synthesised the homochiral hydrazonoyl chlorides **4**. The intramolecular cycloaddition of the corresponding nitrile imines **5** gave the diastereoisomeric 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-6(4*H*)-ones **6** and **7** in enantiopure form.

1. Introduction

Annulated [1,4]benzodiazepines and their oxo-derivatives constitute valuable synthetic targets due to their well-known pharmacological activity as hypnotics and sedatives.[1,2] Among them, pyrazolo[1,5-*a*][1,4]benzodiazepines have been synthesised in a number of ways,[3–6] including the intramolecular nitrile imine cycloaddition route.[7] Even though it would be desirable to obtain such compounds in the enantiomerically pure form, it must be noted that, to date, stereoselective intramolecular cycloadditions of homochiral nitrile imines have been almost entirely neglected, the only report in the field being a paper from our laboratory.[8] This is in contrast to the wide and detailed knowledge about stereoselective cycloadditions of related 1,3-dipolar species, e.g. nitrile oxides[9] and nitrones.[10] The present work is focused on the stereochemical outcome of the intramolecular cycloadditions of nitrile imines **5**, which contain the (*S*)-1-phenylethyl unity.

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2. Results and discussion

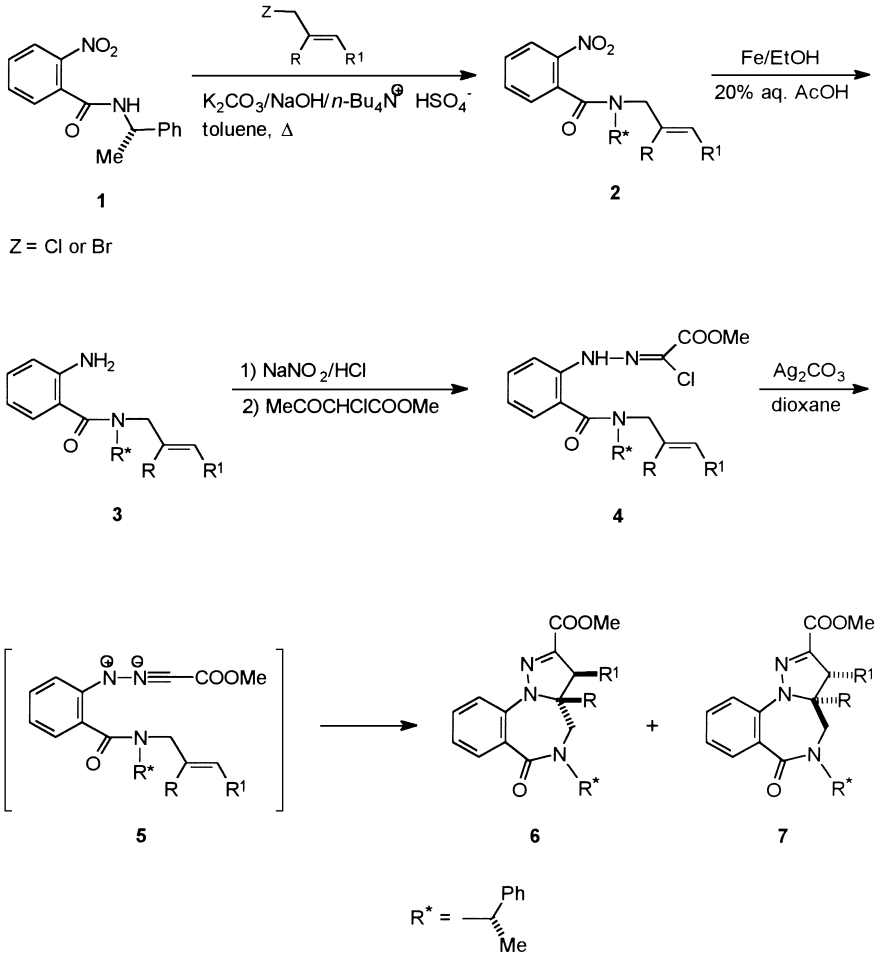
First of all, our approach required the synthesis of enantiopure hydrazonoyl chlorides **4**, which was achieved recognising *N*-[(*S*)-1-phenylethyl]-2-nitrobenzamide **1** as a readily accessible chiral building block (Scheme 1). Nitrile imines **5** were generated in situ by treating the corresponding hydrazonoyl chlorides **4** with a 2:1 molar ratio of silver carbonate in dry dioxane at room temperature, following a well-established procedure elaborated by us.[11] Products and their isolation yields, as well as reaction times and eluants, are collected in Table 1. Besides the recovery of some amounts of the starting hydrazonoyl chlorides, the reaction outcomes were quite satisfactory in terms of the good cycloaddition yields. Furthermore, each diastereoisomeric cycloadduct **6** and **7** was obtained in its enantiomerically pure form by simple column chromatography. For the sake of comparison, nitrile imine **5a** was also generated following the standard triethylamine method (Table 1).

Analytical and spectral data of the cycloaddition products were consistent with the above formulae, but deserve some comments. As far as the ^{1}H NMR is concerned, we focused on the proton situated at the junction of the heterocyclic rings. Minor cycloadducts **7a**,**c**,**d** exhibit resonances in the 4.21–4.41 ppm region, which is in agreement with the literature data for the 5-position of the pyrazolinic ring.[12] Conversely, the signal appears upfielded between 3.15–3.62 ppm within the series of major diastereoisomers **6a**,**c**,**d**. A similar statement applies to the pair **6b** and **7b** having R=Me; minor diastereoisomer **7b** shows the methyl resonance at 1.12 ppm, while the signal is upfielded at 0.73 ppm in the case of major diastereoisomer **6b**. The somewhat anomalous upfielded values could be justified by taking into account the shielding effect induced by the phenyl ring of the chiral pendant. Careful inspection of Dreiding stereomodels indicates that such shielding effects are possible provided that the absolute configuration of the pyrazolinic C-5 is (*R*).

The slow evaporation of a solution of **7a** in chloroform gave crystals in a suitable form for X-ray diffractometric analysis, which revealed the absolute configuration of the pyrazolinic C-5 to be (*S*) (see Fig. 1) in harmony with our expectations on the basis of proton resonance spectra. Even in the solid state, **7a** exists in two distinct crystallographic forms (namely molecules A and A′), which differs for some dihedral angles (see Section 3.7); however, the (*S*) configuration at the pyrazolinic C-5 remains unambiguously defined in both molecules A and A′. Corroborated by the crystallographic evidence, we were confident in assigning the (*S*) configuration to the pyrazolinic C-5 of all cycloadducts **7** and the (*R*) one to the diastereoisomeric products **6**. It remains to be added that the *cis* relationship between R and R^1 (entries **c**, **d**) is dictated by the stereoconservative nature of cycloaddition reactions, and in addition the H–H scalar coupling constants fall in the range 9.2–10.8 Hz and are consistent with the expected *trans* disposition.[13]

As can be inferred from Table 1, intramolecular cycloadditions of labile nitrile imine intermediates **5** proceed with stereoselectivities ranging from fair to good; this is worth noting because the distance between the pre-existing and the newly formed stereocentres is rather large. In the presence of silver carbonate, the cycloadducts ratio **6**:**7** encompasses the range from 60:40 (entry **b**) to 75:25 (entry **c**). Surprisingly, when **4a** was reacted in the presence of triethylamine, a reversal of the stereochemical preference occurred, cycloadduct **7a** being predominant over **6a** (**6a**:**7a**=35:65, entry **e**).

To gain insight about the origin of the observed diastereopreference, we undertook a computational study on nitrile imine **5a**, cycloadducts **6a** and **7a**, and the corresponding transition states **TS6** and **TS7** (Fig. 2). All geometries were fully optimised at the RHF/6-31G and RHF/6-31G* level; in addition, single point calculations were performed at the RHF/6-31G**//RHF/6-31G and RHF/6-31G**//RHF/6-31G* level.[14] The resulting energies are given in Table 2. Notwithstanding cycloadduct **6a** being predicted to be more stable than **7a**, the transition state **TS6** lies higher than the diastereoisomeric one, **TS7**;



entry	a	b	c	d
R	H	Me	H	H
R1	H	H	Me	Ph

Scheme 1.

so that the formation of **7a** is kinetically favoured. Assuming the cancellation of both entropic effect and electronic correlation energy, because of the high electronic and geometric similarity between the competitive transition states, the predicted product ratio **6a**:**7a** at room temperature should be 34:66. This just matches the experimental evidence when using triethylamine, but not when using silver carbonate. In the light of the known coordinative effect of the silver ion toward olefins[15] and aromatic rings,[16] one may suggest a stabilised, complexed transition state, the geometry of which resembles **TS6**.

In conclusion, the present work demonstrates that nitrile imine intermediates **5** are capable of intramolecular cycloadditions onto the ethylenic moiety giving rise to enantiomerically pure 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-6(4*H*)-ones **6** and **7** with good overall yields. Some degree

Table 1
Base-promoted reaction of hydrazonoyl chlorides **4**

Entry	Compd	Base (Equiv.)	Time[a] (h)	Products and yields (%)[b]			Eluant
				4	**6**	**7**	
a	**4a**	Ag_2CO_3 (2)	96	10	60	26	AcOEt - LP[c] (1:2)
b	**4b**	Ag_2CO_3 (2)	160	15	43	28	AcOEt - LP[c] (1:2)
c	**4c**	Ag_2CO_3 (2)	260	18	30	10	AcOEt - *n*-Hexane (1:2)
d	**4d**	Ag_2CO_3 (2)	170	15	43	25	Et_2O - *n*-Hexane (1:5)
e	**4a**	Et_3N (5)	6	7	32	59	AcOEt - LP[c] (1:2)

[a]0.02 M in dry dioxane, r.t. [b]Isolation yield of pure product. [c]LP= light petroleum bp 45-60°C.

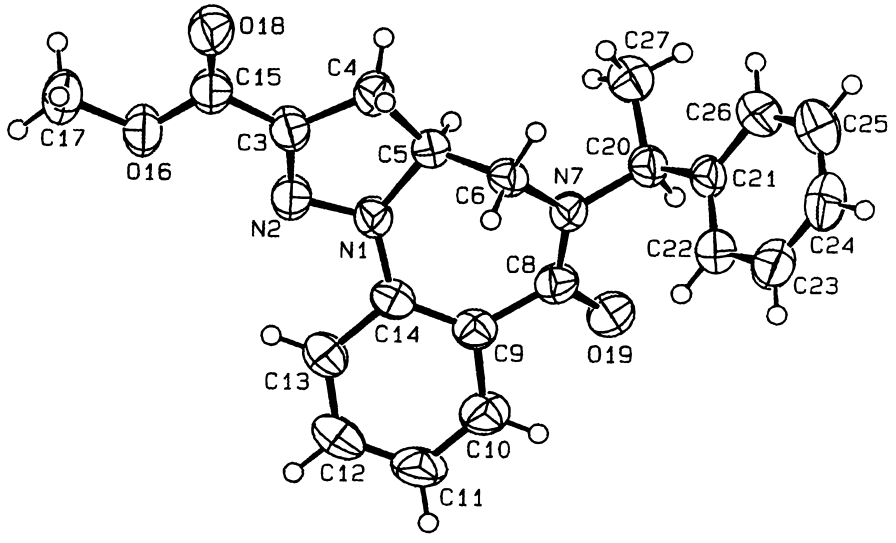
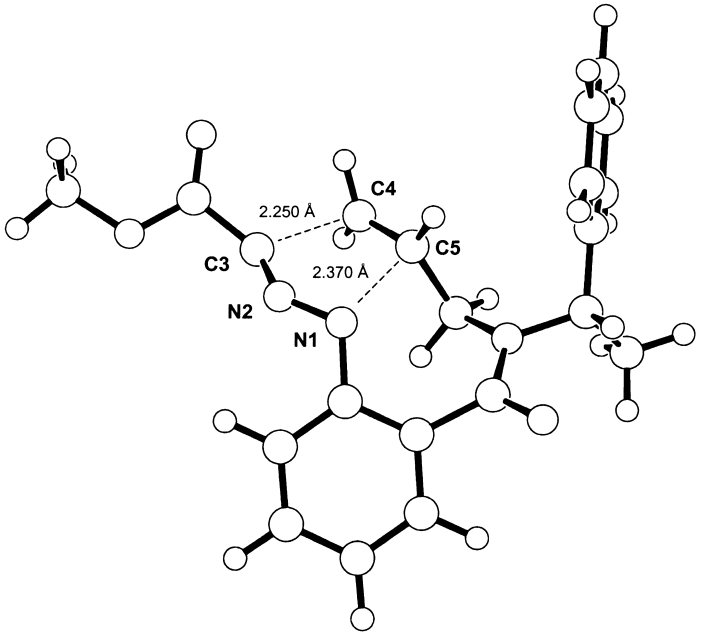


Figure 1. ORTEP plot of **7a** (molecule A) with the crystallographic numbering scheme (the same for molecule A′). Anisotropic displacement parameters are at the 50% probability level. H atoms not to scale

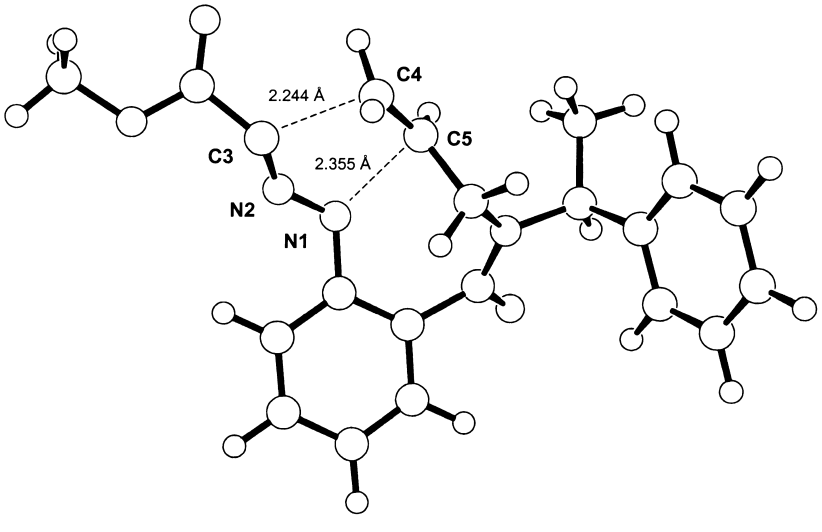
of diastereoselection is operative due to the homochiral α-methylbenzyl pendant. Interestingly, the stereoselectivity of the cycloaddition can be reversed by switching the basic agent.

3. Experimental

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ instrument. ^{1}H NMR spectra were taken with a Bruker AC 300 instrument (in $CDCl_3$ solutions). Chemical shifts are given as ppm from tetramethylsilane and coupling constants are given in hertz.



TS6



TS7

Figure 2. Ab initio RHF/6-31G* computed structures of transition states **TS6** and **TS7**. Only atoms involved in the ring closure are labelled. Computed distances N1–C5 and C3–C4 are also shown

Table 2
Ab initio computed energies *E* of cycloadducts **6a** and **7a** and transition states **TS6** and **TS7**[a]

Theory level	*E* (Kcal mol^{-1})						Predicted Ratio[b]
	(**6a**)	(**7a**)	(**6a**) - (**7a**)	(**TS6**)	(**TS7**)	(**TS6**) - (**TS7**)	**7a:6a**
RHF/6-31G	-78.277	-77.614	-0.663	21.129	20.735	0.394	66:34
RHF/6-31G*//RHF/6-31G	-76.341	-75.759	-0.582	23.725	23.401	0.325	63:37
RHF/6-31G*	-75.992	-75.430	-0.562	23.612	23.550	0.310	63:37
RHF/6-31G**//RHF/6-31G	-75.865	-75.283	-0.582	23.771	23.450	0.321	63:37[c]
RHF/6-31G**//RHF/6-31G*	-75.503	-74.941	-0.561	23.678	23.361	0.317	63:37[c]

[a]With respect to the energy of reactant **5a**, which is taken as zero. [b]Predicted cycloadduct ratio is computed assuming Boltzmann distribution at 298 K. [c]Experimental ratio **7a**:**6a** = 65:35.

Optical rotations, $[\alpha]_D^{25}$, were recorded on a Perkin–Elmer Model 241 polarimeter at the sodium D line.

3.1. *Preparation of* N-*[(S)-1-phenylethyl]-2-nitrobenzamide* ***1***

A solution of (*S*)-1-phenylethylamine (6.00 g, 49.6 mmol) in dry toluene (130 mL) was treated with K_2CO_3 (34.2 g, 0.25 mol). 2-Nitrobenzoyl chloride (9.18 g, 49.6 mmol) in dry toluene (10 mL) was slowly added and the mixture was refluxed for 4 h under vigorous stirring. The undissolved material was filtered off, and the solvent was evaporated under reduced pressure. Crystallisation of the residue from acetone/benzene gave analytically pure **1** (12.1 g, 90% yield), mp 159°C; $[\alpha]_D^{25}$=−49 (MeOH, *c* 0.21); IR (Nujol): 3290, 1640 (cm^{-1}); ^{1}H NMR: δ 1.63 (3H, d, *J*=7.6), 5.40 (1H, dq, *J*=7.8, 7.6), 6.17 (1H, br d, *J*=7.8), 7.25–8.05 (9H, m); MS: *m/z* 270 (M^+). Anal. calcd for $C_{15}H_{14}N_2O_3$: C, 66.64; H, 5.22; N, 11.57. Found: C, 66.71; H, 5.20; N, 11.50.

3.2. *General procedure for the preparation of* N-*alkenyl*-N-*[(S)-1-phenylethyl]-2-nitrobenzamides* ***2***

A solution of **1** (5.00 g, 18.5 mmol) in dry toluene (80 mL) was treated with K_2CO_3 (3.06 g, 22.2 mmol), NaOH (2.81 g, 70.3 mmol) and Bu_4N^+ HSO_4^- (0.82 g, 2.4 mmol). The appropriate alkenyl bromide (entries **a**, **d**) or chloride (entries **b**, **c**) (30.3 mmol) in dry toluene (7.5 mL) was added dropwise at 60°C. The mixture was warmed to 75°C for 4 h, then the undissolved material was filtered off. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum:ethyl acetate, 1:1, affording **2a**–**d** as undistillable oils not analytically pure.

2a (4.87 g, 85% yield); $[\alpha]_D^{25}$=−167.6 (MeOH, *c* 0.30); IR (neat): 1640 (cm^{-1}); ^{1}H NMR: δ 1.58 (3H, d, *J*=7.0), 3.42 (1H, dddd, *J*=16.7, 6.7, 2.8, 1.4), 3.53 (1H, dddd, *J*=16.7, 6.7, 2.8, 1.4), 4.38–4.78 (2H, m), 5.32 (1H, dddd, *J*=17.0, 16.7, 9.4, 6.7), 6.17 (1H, q, *J*=7.0), 7.30–8.20 (9H, m); MS: *m/z* 310 (M^+).

2b (2.10 g, 35% yield); $[\alpha]_D^{25}$=−44.2 (MeOH, *c* 0.20); IR (neat): 1640 (cm^{-1}); ^{1}H NMR: δ 1.30 (3H, s), 1.58 (3H, d, *J*=7.0), 3.41 (2H, AB, *J*=17.1), 4.52 (1H, d, *J*=2.6), 4.62 (1H, d, *J*=2.6), 5.98 (1H, q, *J*=7.0), 7.30–8.20 (9H, m); MS: *m/z* 324 (M^+).

2c (5.75 g, 96% yield); $[\alpha]_D^{25}$=−108 (MeOH, *c* 0.84); IR (neat): 1640 (cm^{-1}); ^1H NMR: δ 1.34 (3H, d, *J*=7.0), 1.65 (3H, d, *J*=7.2), 3.33 (1H, dd, *J*=16.3, 6.6), 3.42 (1H, dd, *J*=16.3, 6.3), 4.75–4.95 (2H, m), 6.15 (1H, q, *J*=7.2), 7.20–8.20 (9H, m); MS: *m/z* 324 (M^+).

2d (5.71 g, 80% yield); $[\alpha]_D^{25}$=−76.0 (MeOH, *c* 0.10); IR (neat): 1640 (cm^{-1}); ^1H NMR: δ 1.73 (3H, d, *J*=7.0), 3.52 (1H, dd, *J*=17.0, 6.8), 3.67 (1H, dd, *J*=17.0, 6.5), 5.50–5.65 (2H, m), 6.26 (1H, q, *J*=7.0), 7.25–8.20 (14H, m); MS: *m/z* 386 (M^+).

3.3. General procedure for the preparation of N-*alkenyl*-N-*[(S)-1-phenylethyl]-2-aminobenzamides* ***3***

A solution of **2** (10.0 mmol) in ethanol (12 mL) was treated with iron dust (4.47 g, 80 mmol) and 20% aqueous acetic acid (5.0 mL), and then refluxed for 3.5 h under vigorous stirring. The mixture was taken up with ethyl acetate (75 mL) and filtered over Celite. The organic layer was washed firstly with 5% aqueous sodium hydrogen carbonate (80 mL), then with water (2×50 mL), and dried over sodium sulfate.

Evaporation of the solvent gave **3** as undistillable oils not analytically pure.

3a (2.41 g, 86% yield); $[\alpha]_D^{25}$=−20.9 (MeOH, *c* 0.16); IR (neat): 3340, 1620 (cm^{-1}); ^1H NMR: δ 1.62 (3H, d, *J*=7.3), 3.46 (1H, dd, *J*=15.8, 5.8), 4.01 (1H, dd, *J*=15.8, 5.1), 4.75 (2H, br s), 4.90–5.10 (2H, m), 5.40–5.60 (1H, m), 5.72 (1H, q, *J*=7.3), 6.65–7.30 (9H, m); MS: *m/z* 280 (M^+).

3b (2.64 g, 90% yield); $[\alpha]_D^{25}$=−137.5 (MeOH, *c* 0.08); IR (neat): 3330, 1615 (cm^{-1}); ^1H NMR: δ 1.58 (3H, s), 1.60 (3H, d, *J*=7.2), 3.28 (2H, AB, *J*=16.0), 4.30–4.50 (2H, m), 4.75 (2H, br s), 5.50 (1H, q, *J*=7.2), 6.70–7.40 (9H, m); MS: *m/z* 294 (M^+).

3c (2.38 g, 81% yield); $[\alpha]_D^{25}$=−122 (MeOH, *c* 0.52); IR (neat): 3340, 1620 (cm^{-1}); ^1H NMR: δ 1.52 (3H, d, *J*=4.2), 1.61 (3H, d, *J*=7.0), 3.42 (2H, dd, *J*=15.7, 5.4), 3.89 (1H, dd, *J*=15.7, 3.8), 4.25 (2H, br s), 5.25–5.60 (3H, m), 6.70–7.30 (9H, m); MS: *m/z* 294 (M^+).

3d (3.20 g, 90% yield); $[\alpha]_D^{25}$=−82.0 (MeOH, *c* 0.14); IR (neat): 3340, 1620 (cm^{-1}); ^1H NMR: δ 1.76 (3H, d, *J*=7.2), 3.78 (1H, dd, *J*=15.6, 6.6), 4.12 (1H, dd, *J*=15.6, 6.0), 4.70 (2H, br s), 5.58 (1H, q, *J*=7.2), 6.00–6.18 (2H, m), 6.80–7.30 (14H, m); MS: *m/z* 356 (M^+).

3.4. General procedure for the preparation of hydrazonyl chlorides ***4***

A solution of **3** (5.5 mmol) in 6 M aqueous hydrochloric acid (3.2 mL) and methanol (3.0 mL) was cooled to 0°C. Sodium nitrite (0.76 g, 11.0 mmol) was added portionwise keeping the temperature between 0 and 5°C. After 30 min, the pH was adjusted to 5 by adding sodium acetate, and a solution of methyl 2-chloroacetoacetate (0.83 g, 5.5 mmol) in methanol (1.5 mL) was added under vigorous stirring and ice-cooling. The mixture was allowed to stand overnight under stirring at room temperature. The solvent was partly removed under reduced pressure and the resulting mixture was extracted with diethyl ether (75 mL). The organic layer was washed firstly with 5% sodium hydrogen carbonate (25 mL), then with water (75 mL), and dried over sodium sulfate. The residue was chromatographed on a silica gel column with diethyl ether to give the hydrazonyl chlorides **4** as undistillable oils not analytically pure.

4a (1.69 g, 77% yield); $[\alpha]_D^{25}$=−46.0 (MeOH, *c* 0.25); IR: 3280, 1730, 1620 (cm^{-1}); ^1H NMR: δ 1.65 (3H, d, *J*=7.1), 3.52 (1H, dd, *J*=16.5, 5.9), 3.91 (3H, s), 4.10 (1H, dd, *J*=16.5, 4.7), 4.80–5.10 (2H, m), 5.56 (1H, q, *J*=7.1), 5.58–5.90 (1H, m), 6.90–7.70 (9H, m), 9.65 (1H, br s); MS: *m/z* 399 (M^+).

4b (1.86 g, 82% yield); $[\alpha]_D^{25}$=−27.7 (MeOH, *c* 0.044); IR: 3270, 1730, 1625 (cm^{-1}); ^1H NMR: δ 1.55 (3H, s), 1.66 (3H, d, *J*=7.1), 3.38 (2H, AB, *J*=16.0), 3.93 (3H, s), 4.76 (1H, d, *J*=2.1), 4.84 (1H, d, *J*=2.1), 5.54 (1H, q, *J*=7.1), 6.95–7.70 (9H, m), 9.80 (1H, br s); MS: *m/z* 413 (M^+).

4c (1.20 g, 53% yield); $[\alpha]_D^{25}$=−37.0 (MeOH, *c* 0.12); IR: 3270, 1730, 1645 (cm^{-1}); ^1H NMR: δ 1.52 (3H, br d), 1.66 (3H, d, *J*=7.2), 3.48 (1H, d, *J*=4.0), 3.54 (1H, d, *J*=3.1), 3.93 (3H, s), 5.20–5.80 (3H, m), 6.90–7.20 (9H, m), 9.60 (1H, br s); MS: *m/z* 413 (M^+).

4d (1.96 g, 75% yield); $[\alpha]_D^{25}$=−58.0 (MeOH, *c* 0.06); IR: 3270, 1735, 1620 (cm^{-1}); ^1H NMR: δ 1.80 (3H, d, *J*=7.1), 3.78 (1H, dd, *J*=15.8, 6.0), 3.96 (3H, s), 4.24 (1H, dd, *J*=1.8, 4.8), 5.60–6.10 (2H, m), 6.20 (1H, q, *J*=7.1), 7.05–7.75 (14H, m), 9.60 (1H, br s); MS: *m/z* 475 (M^+).

*3.5. General procedure for the reaction of hydrazonyl chlorides **4** with silver carbonate*

A solution of the hydrazonyl chlorides **4** (2.5 mmol) in dry dioxane (125 mL) was treated with silver carbonate (1.38 g, 5.0 mmol), and stirred in the dark at room temperature for the time indicated in Table 1. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column. Unreacted hydrazonoyl chlorides **4** were eluted first. Further elution gave **6**, followed by **7**. Isolation yields and eluents are collected in Table 1. All compounds were obtained in an analytically pure state by recrystallisation.

6a (0.54 g, 60% yield) mp 145°C (from diisopropyl ether); $[\alpha]_D^{25}$=−26.5 (MeOH, *c* 0.20); IR: 1725, 1625 (cm^{-1}); ^1H NMR: δ 1.50 (3H, d, *J*=7.0), 2.62 (1H, dd, *J*=18.1, 11.7), 2.80 (1H, dd, *J*=18.1, 12.5), 3.26 (1H, dd, *J*=14.5, 0.9), 3.38 (1H, dd, *J*=14.5, 7.2), 3.51–3.62 (1H, m), 3.92 (3H, s), 6.20 (1H, q, *J*=7.0), 7.02–8.08 (9H, m); MS: *m/z* 363 (M^+). Anal. calcd for $C_{21}H_{21}N_3O_3$: C, 69.39; H, 5.83; N, 11.57. Found: C, 69.44; H, 5.88; N, 10.36.

7a (0.24 g, 26% yield) mp 89°C (from diisopropyl ether); $[\alpha]_D^{25}$=+678 (MeOH, *c* 0.20); IR: 1725, 1625 (cm^{-1}); ^1H NMR: δ 1.60 (3H, d, *J*=7.0), 2.77 (1H, dd, *J*=18.0, 11.4), 3.14 (1H, dd, *J*=15.0, 0.7), 3.23 (1H, dd, *J*=15.0, 8.4), 3.38 (1H, dd, *J*=18.0, 12.5), 3.85 (3H, s), 4.24–4.37 (1H, m), 6.22 (1H, q, *J*=7.0), 7.03–8.18 (9H, m); MS: *m/z* 363 (M^+). Anal. calcd for $C_{21}H_{21}N_3O_3$: C, 69.39; H, 5.83; N, 11.57. Found: C, 69.41; H, 5.77; N, 10.22.

6b (0.37 g, 39% yield) mp 140°C (from diisopropyl ether); $[\alpha]_D^{25}$=−213 (MeOH, *c* 0.12); IR: 1700, 1610 (cm^{-1}); ^1H NMR: δ 0.73 (3H, s), 1.58 (3H, d, *J*=7.2), 2.83 (1H, d, *J*=17.3), 3.13 (1H, d, *J*=17.3), 3.17 (1H, d, *J*=15.2), 3.34 (1H, d, *J*=15.2), 3.82 (3H, s), 6.38 (1H, q, *J*=7.2), 7.10–8.20 (9H, m); MS: *m/z* 377 (M^+). Anal. calcd for $C_{22}H_{23}N_3O_3$: C, 69.99; H, 6.15; N, 11.14. Found: C, 70.08; H, 6.21; N, 11.20.

7b (0.25 g, 26% yield) mp 73°C (from diisopropyl ether); $[\alpha]_D^{25}$=+67.0 (MeOH, *c* 0.08); IR: 1703, 1620 (cm^{-1}); ^1H NMR: δ 1.12 (3H, s), 1.58 (3H, d, *J*=7.0), 2.16 (1H, d, *J*=17.3), 2.59 (1H, d, *J*=17.3), 3.18 (1H, d, *J*=15.3), 3.28 (1H, d, *J*=15.3), 3.83 (3H, s), 6.17 (1H, q, *J*=7.0), 7.20–8.10 (9H, m); MS: *m/z* 377 (M^+). Anal. calcd for $C_{22}H_{23}N_3O_3$: C, 69.99; H, 6.15; N, 11.14. Found: C, 70.03; H, 6.11; N, 11.11.

6c (0.28 g, 30% yield) mp 122°C (from methanol); $[\alpha]_D^{25}$=−328 (MeOH, *c* 0.12); IR: 1720, 1620 (cm^{-1}); ^1H NMR: δ 0.70 (3H, d, *J*=6.9), 1.53 (3H, d, *J*=7.1), 2.95 (1H, qd, *J*=10.6, 6.9), 3.15–3.26 (2H, m), 3.34 (1H, dd, *J*=14.8, 7.6), 3.82 (3H, s), 6.45 (1H, q, *J*=7.1), 7.04–8.18 (9H, m); MS: *m/z* 377 (M^+). Anal. calcd for $C_{22}H_{23}N_3O_3$: C, 69.99; H, 6.15; N, 11.14. Found: C, 70.05; H, 6.19; N, 11.22.

7c (24 mg, 10% yield) mp 75°C (from methanol); $[\alpha]_D^{25}$=+430 (MeOH, *c* 0.16); IR: 1710, 1625 (cm^{-1}); ^1H NMR: δ 1.03 (3H, d, *J*=7.2), 1.62 (3H, d, *J*=7.0), 3.27 (1H, dd, *J*=15.7, 8.3), 3.37 (1H, dd, *J*=15.7, 1.3), 3.46 (1H, qd, *J*=10.6, 7.2), 3.87 (3H, s), 4.41 (1H, ddd, *J*=10.6, 8.7, 1.0), 6.30 (1H, q, *J*=7.0), 7.05–8.08 (9H, m); MS: *m/z* 377 (M^+). Anal. calcd for $C_{22}H_{23}N_3O_3$: C, 69.99; H, 6.15; N, 11.14. Found: C, 70.08; H, 6.11; N, 11.21.

6d (0.42 g, 38% yield) mp 185°C (from methanol); $[\alpha]_D^{25}$=−487 (MeOH, *c* 0.24); IR: 1720, 1620 (cm^{-1}); ^1H NMR: δ 1.50 (3H, d, *J*=7.1), 3.31 (1H, dd, *J*=14.6, 0.8), 3.44 (1H, dd, *J*=14.6, 7.5), 3.62 (1H, ddd, *J*=9.2, 7.5, 0.8), 3.68 (3H, s), 4.02 (1H, d, *J*=9.2), 6.35 (1H, q, *J*=7.1), 6.95–8.22 (14H, m); MS: *m/z* 439 (M^+). Anal. calcd for $C_{27}H_{25}N_3O_3$: C, 73.33; H, 5.74; N, 9.57. Found: C, 73.39; H, 5.78; N, 9.66.

7d (0.24 g, 22% yield) mp 80°C (from methanol); $[\alpha]_D^{25}$=+612 (MeOH, *c* 0.44); IR: 1710, 1624 (cm^{-1}); ^1H NMR: δ 1.22 (3H, d, *J*=7.0), 3.22 (1H, dd, *J*=15.7, 1.6), 3.33 (1H, dd, *J*=15.7, 6.5), 3.73 (3H, s), 4.13 (1H, d, *J*=10.8), 4.21 (1H, ddd, *J*=10.8, 6.5, 1.6), 6.12 (1H, q, *J*=7.0), 7.10–8.15 (14H, m); MS: *m/z* 439 (M^+). Anal. calcd for $C_{27}H_{25}N_3O_3$: C, 73.33; H, 5.74; N, 9.57. Found: C, 73.30; H, 5.70; N, 9.53.

3.6. Reaction of hydrazonyl chloride ***4a*** with triethylamine

A solution of **4a** (1.00 g, 2.5 mmol) in dry dioxane (125 mL) was treated with triethylamine (1.26 g, 12.5 mmol), and stirred at room temperature for the time indicated in Table 1. The solvent was evaporated, and then the residue was chromatographed on a silica gel column. Products, isolation yields and eluants are collected in Table 1.

3.7. X-Ray structure determination of ***7a***

$C_{21}H_{21}N_3O_3$, monoclinic, space group *I*2, M_r=363.41, *a*=28.331(3), *b*=7.4968(4), *c*=17.4630(14) Å, β=90.947(8)°, *V*=3708.5(5) $Å^3$, room temperature [291(1) K], *Z*=8, d_{calc}=1.302 g cm^{-1}, μ(Mo*K*α)=0.089 mm^{-1}; Siemens P4 diffractometer, Mo*K*α radiation, λ=0.71073 Å. Data collection: ω/2θ scans, $4.5<2\theta<55.0°$; $-36<h<1$, $-1<k<9$, $-22<l<22$; 5533 reflections collected, 5230 independent, 3697 with $I>2\sigma(I)$, averaging *R*=0.0100. The structure was solved by *SIR*92,[17] and refined on F^2 by full-matrix least-squares using SHELX97.[18] Heavy atoms anisotropic, H atoms isotropic, final discrepancy indexes based on F^2: *R*=0.0372 (0.0637 for all 5230 reflections) and w*R*=0.0710 (0.0793), g.o.f. 1.003; difference map ranges from −0.11 to 0.11 e $Å^{-3}$. Absolute configuration was based on knowledge of the reactant's [(*S*)-1-phenylethylamine]. The main differences between the two independent molecules A and A′ are due relative to the torsion angles: the more relevant are N2–C3–C15–O18 [−2.3(4) and 172.6(3)° for molecule A and A′, respectively] and C8–N7–C20–C27 [127.9(2) and 99.5(3)° for A and A′, respectively]; other differences, greater than 10° are found for some torsion angles around the bonds N2–N1, N1–C5, N1–C14, N7–C8 and N7–C20. These differences can be explained only by the different environment of the two independent molecules.

3.8. Ab initio calculations

All calculations have been performed by means of Sun Ultra Enterprise workstations running the program suite Gaussian 94.[19] Ab initio restricted Hartree–Fock (RHF) calculations were carried out using the 6-31G, 6-31G* and 6-31G** basis sets. Because of the large size of the studied molecules (48 atoms, 192 electrons), stationary points (energy minima and transition states) were fully optimised by analytical gradient techniques only with the RHF/6-31G and RHF/6-31G* basis sets. Transition state structures (with one negative eigenvalue of the second-derivatives matrix) were obtained by the quadratic synchronous transit search method QST2.[20] Single-point calculations at the optimised geometries were performed with the RHF/6-31G** basis set.

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