Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4447–4454

TETRAHEDRON:
ASYMMETRY

Asymmetric induction by the (*S*)-1-phenylethyl group in intramolecular nitrile imine cycloadditions giving enantiopure 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones

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Received 22 October 1999; accepted 4 November 1999

Abstract

Stereoselective intramolecular cycloadditions of homochiral nitrile imines **5** are described as a fruitful source of enantiopure 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones **6** and **7**.

1. Introduction

The synthesis of enantiomerically pure molecules from simple starting materials represents a major challenge in contemporary organic chemistry and nearly all organic reactions,[1] including 1,3-dipolar cycloadditions,[2] have been exploited for this purpose. However, the available examples of stereoselective intramolecular cycloadditions of homochiral nitrile imines are still rare, the only contribution being represented by three recent papers from our laboratory.[3–5] In continuing our research in this field, we report here on the synthesis of enantiopure pyrazolo[1,5-*a*][1,4]benzodiazepine-4-ones **6** and **7**, which are of potential pharmacological interest.[6] The inexpensive, commercially available (*S*)-1-phenylethylamine was used as the starting homochiral unit.

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0957-4166/99/$ - see front matter
PII: S0957-4166(99)00493-0

2. Results and discussion

N-[(*S*)-1-Phenylethyl]-2-nitrobenzylamine **1**, which we considered to be the fundamental chiral building block, was readily obtained by reacting (*S*)-1-phenylethylamine with 2-nitrobenzyl chloride. The enantiopure hydrazonoyl chlorides **4** were then synthesised as depicted in Scheme 1. The in situ generation of the desired nitrile imines **5** was accomplished by treating a 0.02 M solution of **4** with a twofold molar excess of silver carbonate in dry dioxane at room temperature. Products and their isolated yields, as well as reaction times and eluants, are collated in Table 1. The material yields of the intramolecular cycloadditions were extremely satisfactory, since the overall yields were practically quantitative. Furthermore, a simple column chromatography of the reaction mixtures allowed the clean separation of the pure diastereoisomeric cycloadducts **6** and **7** in the pure state. In order to test the influence of the basic medium on reactivity, the generation of nitrile imine **5a** was also accomplished by treating a 0.02 M solution of **4a** with an excess of triethylamine in dry dioxane at room temperature.

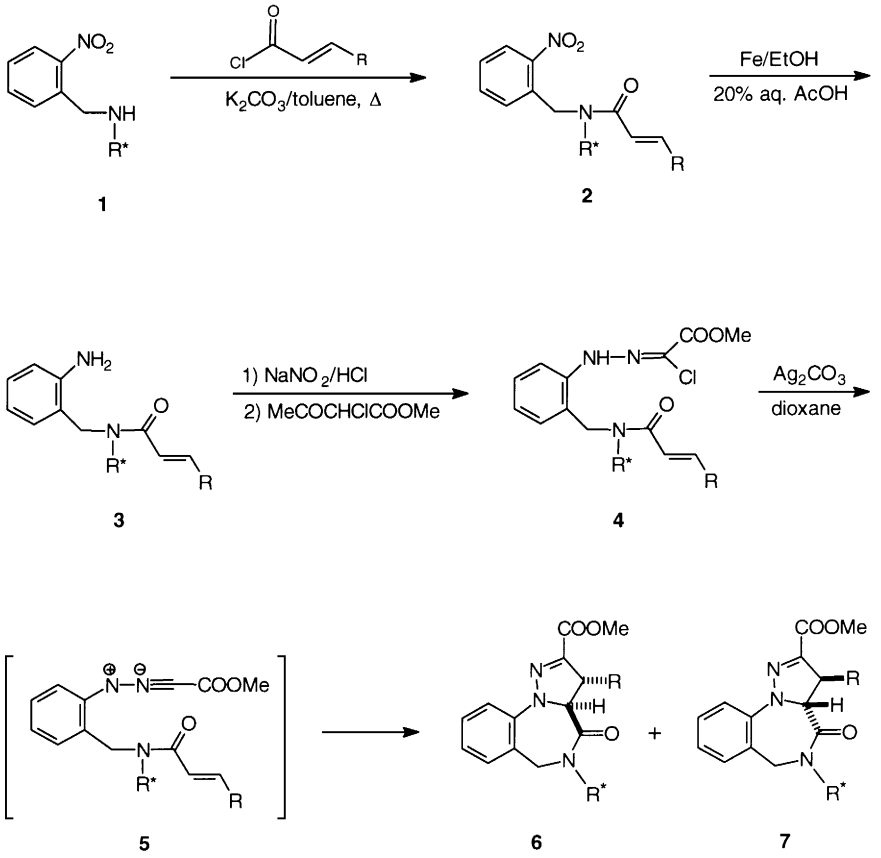
Table 1
Base-promoted reaction of hydrazonoyl chlorides **4**

Entry	Compd	Base (Equiv.)	Time[a] (h)	Products and yields (%)[b]		Eluant
				6	**7**	
a	**4a**	Ag_2CO_3 (2)	52	75	21	AcOEt - *n*-Hexane (2:1)
b	**4b**	Ag_2CO_3 (2)	140	61	33	Et_2O - *n*-Hexane (2:1)
c	**4c**	Ag_2CO_3 (2)	140	69	27	Et_2O - *n*-Hexane (1:2)
d	**4a**	Et_3N (5)	24	52	20	AcOEt - *n*-Hexane (1:3)

[a]0.02 M in dry dioxane, r.t. [b]Isolation yield of pure product.

Structural assignments of the above cycloadducts rely upon analytical and spectroscopic data. In particular, the ^{1}H NMR spectra of the minor diastereoisomers **7** show the upfielded resonance of the two aromatic hydrogens in the 7 and 8 positions. The fact that these signals fall in the range 5.61–6.52 δ can be justified by assuming a shielding effect exerted by the phenyl ring of the chiral pendant moiety. This shielding effect, which is lacking in the case of major diastereoisomers **6**, may be related to the absolute configuration of the stereocentre in the 5-position of the pyrazolinic ring. In fact, careful inspection of Dreiding molecular stereomodels revealed that the mentioned hydrogens are shielded when the absolute configuration of the pyrazolinic C-5 is (*R*). In the cases where R≠H, the *trans* relationship between the hydrogens in the 4- and 5-positions of the pyrazolinic ring, which was predictable on the basis of the concerted nature of the cycloadditions,[7] is substantiated by the H–H scalar coupling constants, whose values encompass the range from 6.3 to 6.8 Hz.[8]

The X-ray crystallographic analysis of all minor diastereoisomers **7** further supported the above assignments. As can be viewed from the ORTEPIII[9] description in Fig. 1, the spatial orientation of the phenyl ring of the chiral auxiliary accounts for the observed upfielded resonance. Furthermore, the (*R*) absolute configuration to the pyrazolinic C-5 of all minor cycloadducts **7** was unambiguously demonstrated and consequently the (*S*) absolute configuration was assigned to the major cycloadducts **6**.



entry	a	b	c
R	H	Me	Ph

Scheme 1.

As far as diastereoselection is concerned, intramolecular cycloadditions of nitrile imines **5** display some preference for diastereoisomers **6**. The ratio **6**:**7**, encompassing the range from 78:22 (entry a) to 65:35 (entry b), is remarkable considering that the distance between the chiral auxiliary and the newly formed stereocentres is rather large.

As can be seen from entries a and d in Table 1, the behaviour of nitrile imine **5a** in terms of stereoselection is almost independent of the complexing nature of the basic agent, the cycloadduct ratio **6a**:**7a** being roughly the same on going from silver carbonate to triethylamine. This means that although metallated transition states are conceivable in light of the known complexing ability of the silver ion towards olefins[10] and aromatic rings,[11] they must be geometrically similar to the metal-free ones. Such a fact is worthy to note since the intramolecular cycloaddition of a structurally related nitrile imine, recently reported by us,[4] actually reverses the diastereoselectivity as a function of the basic agent.

In conclusion, we have found that the good dipolarophilic character of the α,β-unsaturated amide fragment makes the intramolecular cycloadditions of nitrile imines **5** very efficient and, hence, valuable

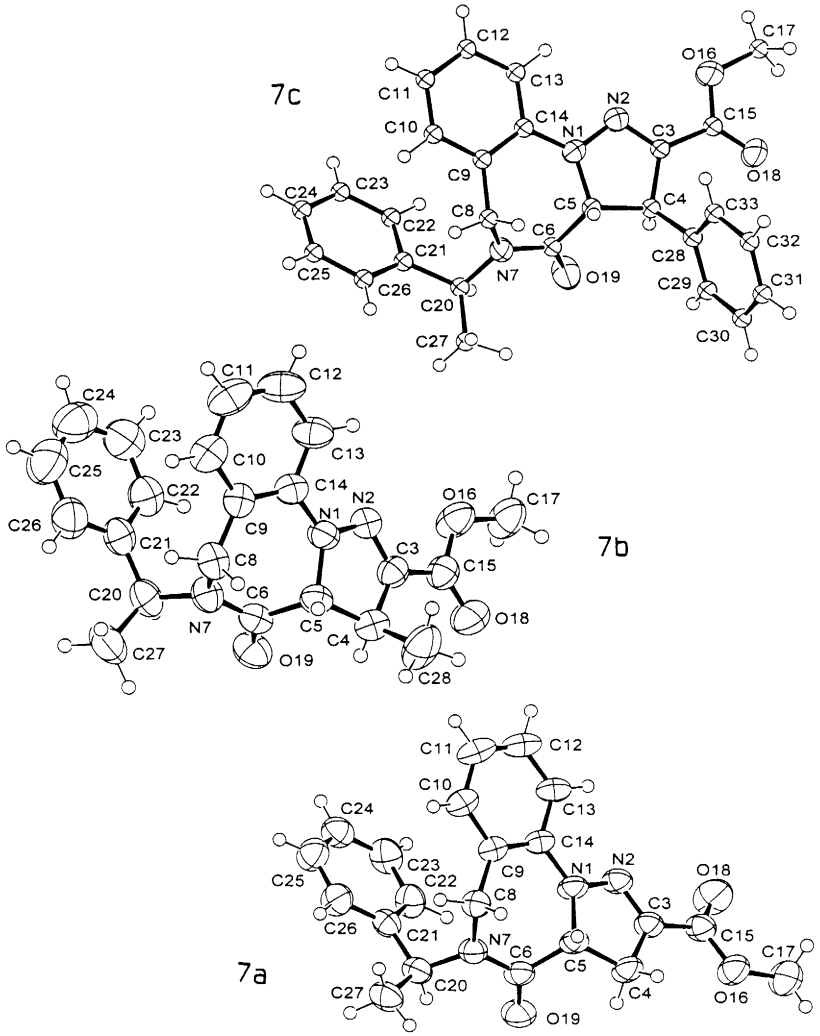


Fig. 1. ORTEPIII[9] projection of **7a**, **7b** and **7c** with the crystallographic numbering scheme. As can be see the numbering is the same for the common moiety. Ellipsoids at 50% probability level. H atoms not to scale.

on a preparative scale. The easy separation of cycloadducts **6** and **7** allows the multi-gram synthesis of enantiopure 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepin-4(6*H*)-ones.

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 apparatus. ^{1}H NMR spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in hertz. 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-nitrobenzylamine **1**

A solution of (*S*)-1-phenylethylamine (5.00 g, 41.3 mmol) in dry toluene (50 mL) was added to potassium iodide (1.37 g, 8.3 mmol). 2-Nitrobenzyl chloride (3.53 g, 20.6 mmol) in dry toluene (5 mL) was slowly added and the mixture was refluxed for 3 h under vigorous stirring. Toluene (25 mL) was added, the white precipitate was filtered off, and the solvent was evaporated under reduced pressure. Crystallisation of the residue from diisopropyl ether gave analytically pure **1** (3.70 g, 70%), mp 159°C; $[\alpha]_D^{25}=-10.2$ (MeOH, c=0.40); IR (Nujol): 3350 (cm^{-1}); ^1H NMR δ: 1.38 (3H, d, *J* 6.6), 1.90 (1H, br s), 3.81 (1H, q, *J* 6.6), 3.83 (1H, d, *J* 14.0), 3.88 (1H, d, *J* 14.0), 7.20–7.95 (9H, m); MS: *m/z* 256 (M^+). Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.28; H, 6.30; N, 10.93. Found: C, 70.35; H, 6.33; N, 11.01.

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

A solution of **1** (5.00 g, 19.5 mmol) in dry toluene (140 mL) was added to K_2CO_3 (5.38 g, 39.0 mmol). The appropriate alkenyol chloride (19.5 mmol) in dry toluene (5.0 mL) was added dropwise at 90°C. The mixture was refluxed for 4 h, then the undissolved material was filtered off. The organic layer was washed with water (50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on a silica gel column with diethyl ether:dichloromethane 10:1 affording **2a**–**d** as undistillable oils, not analytically pure.

Compound **2a** (5.44 g, 90%) as a pale yellow oil; $[\alpha]_D^{25}=-34.6$ (MeOH, c=0.33); IR (neat): 1650 (cm^{-1}); ^1H NMR δ: 1.52 (3H, d, *J* 7.0), 4.65 (1H, d, *J* 17.1), 4.95 (1H, d, *J* 17.1), 5.68 (1H, q, *J* 7.0), 6.00–6.60 (3H, m), 7.15–7.95 (9H, m); MS: *m/z* 310 (M^+).

Compound **2b** (5.50 g, 87%) as a pale yellow oil; $[\alpha]_D^{25}=-48.4$ (MeOH, c=0.27); IR (neat): 1660 (cm^{-1}); ^1H NMR δ: 1.50 (3H, d, *J* 7.0), 1.80 (3H, d, *J* 6.5), 4.70 (1H, d, *J* 17.4), 4.88 (1H, d, *J* 17.4), 5.46 (1H, q, *J* 7.0), 5.90–6.50 (2H, m), 7.20–7.95 (9H, m); MS: *m/z* 324 (M^+).

Compound **2c** (6.55 g, 87%) as a yellow oil; $[\alpha]_D^{25}=-98.0$ (MeOH, c=0.12); IR (neat): 1650 (cm^{-1}); ^1H NMR δ: 1.51 (3H, d, *J* 7.1), 4.85 (1H, d, *J* 18.0), 5.00 (1H, d, *J* 18.0), 5.57 (1H, q, *J* 7.1), 6.30 (1H, d, *J* 16.2), 6.52 (1H, d, *J* 16.2), 7.20–7.90 (14H, m); MS: *m/z* 386 (M^+).

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

A solution of **2** (15.0 mmol) in ethanol (20 mL) was treated with iron powder (5.96 g, 0.11 mol) and 20% aqueous acetic acid (7.5 mL), and then refluxed for 3 h under vigorous stirring. The mixture was taken up with ethyl acetate (100 mL) and filtered over Celite. The organic layer was washed firstly with 5% aqueous sodium hydrogencarbonate (40 mL), then with water (2×50 mL), and dried over sodium sulfate. Evaporation of the solvent gave **3** as undistillable oils, not analytically pure.

Compound **3a** (3.86 g, 92%) as colourless oil; $[\alpha]_D^{25}=-73.0$ (MeOH, c=0.10); IR (neat): 3435, 3350, 3240, 1645 (cm^{-1}); ^1H NMR δ: 1.51 (3H, d, *J* 6.5), 4.25 (1H, d, *J* 15.6), 4.50 (2H, br s), 4.93 (1H, d, *J* 15.6), 5.52 (1H, q, *J* 6.5), 6.20–6.50 (3H, m), 6.65–7.30 (9H, m); MS: *m/z* 280 (M^+).

Compound **3b** (4.13 g, 94%) as colourless oil; $[\alpha]_D^{25}=-109.0$ (MeOH, c=0.28); IR (neat): 3440, 3350, 3235, 1660 (cm^{-1}); ^1H NMR δ: 1.45 (3H, d, *J* 6.6), 1.78 (3H, d, *J* 7.5), 3.45 (1H, d, *J* 15.8), 4.15 (2H, br s), 4.90 (1H, d, *J* 15.8), 5.20 (1H, q, *J* 6.6), 6.00–7.35 (11H, m); MS: *m/z* 294 (M^+).

Compound **3c** (5.07 g, 95%) as colourless oil; $[\alpha]_D^{25}=-41.3$ (MeOH, c=0.17); IR (neat): 3435, 3345, 3230, 1645 (cm^{-1}); ^1H NMR δ: 1.58 (3H, d, *J* 7.0), 4.35 (1H, d, *J* 14.9), 4.68 (2H, br s), 5.02 (1H, d, *J* 14.9), 5.10 (1H, q, *J* 7.0), 6.50–7.30 (16H, m); MS: *m/z* 356 (M^+).

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

A solution of **3** (7.5 mmol) in 6 M aqueous hydrochloric acid (4.5 mL) and methanol (5.0 mL) was cooled to 3°C. Sodium nitrite (1.04 g, 15.0 mmol) was added portionwise keeping the temperature between 0 and 5°C. After 15 min, the pH was adjusted to 5 by adding sodium acetate, and a solution of methyl 2-chloroacetoacetate (1.13 g, 7.5 mmol) in methanol (2.0 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 hydrogencarbonate (20 mL), then with water (50 mL), and dried over sodium sulfate. Evaporation of the solvent gave crude hydrazonyl chlorides **4** as undistillable oils.

Compound **4a** (2.69 g, 90%) as pale yellow oil; IR (neat): 3165, 1730, 1640 (cm^{-1}); ^1H NMR δ: 1.59 (3H, d, *J* 7.2), 3.95 (3H, s), 4.40 (1H, d, *J* 15.1), 4.73 (1H, d, *J* 15.1), 5.23 (1H, q, *J* 7.2), 5.60–6.40 (3H, m), 6.75–7.60 (9H, m), 10.60 (1H, br s).

Compound **4b** (2.78 g, 90%) as pale yellow oil; IR (neat): 3160, 1732, 1660 (cm^{-1}); ^1H NMR δ: 1.60 (3H, d, *J* 6.7), 1.80 (3H, d, *J* 6.3), 3.92 (3H, s), 4.35 (1H, d, *J* 15.0), 4.68 (1H, d, *J* 15.0), 5.25 (1H, q, *J* 6.7), 6.16 (1H, d, *J* 15.4), 6.87 (1H, d, *J* 15.4), 6.95–7.55 (9H, m), 11.70 (1H, br s).

Compound **4c** (3.35 g, 94%) as yellow oil; IR (neat): 3160, 1730, 1645 (cm^{-1}); ^1H NMR δ: 1.64 (3H, d, *J* 6.8), 3.91 (3H, s), 4.48 (1H, d, *J* 15.1), 4.83 (1H, d, *J* 15.1), 5.29 (1H, q, *J* 6.8), 6.65 (1H, d, *J* 15.3), 6.86–7.60 (14H, m), 7.70 (1H, d, *J* 15.3), 11.80 (1H, br s).

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

A solution of **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 purified by chromatography on a silica gel column. Major diastereoisomer **6** was eluted first, followed by the minor diastereoisomer **7**. Products, isolation yields and eluants are collected in Table 1. All compounds were obtained in analytically pure state by recrystallisation.

Compound **6a** (0.68 g, 75%), mp 158°C (from diisopropyl ether); $[\alpha]_D^{25}=+105.8$ (MeOH, c=0.11); IR (Nujol): 1730, 1640 (cm^{-1}); ^1H NMR δ: 1.37 (3H, d, *J* 7.1), 3.27 (1H, dd, *J* 18.1, 13.5), 3.75 (1H, d, *J* 17.1), 3.89 (3H, s), 4.18 (1H, dd, *J* 18.1, 8.5), 4.76 (1H, d, *J* 17.1), 5.69 (1H, dd, *J* 13.5, 8.5), 6.02 (1H, q, *J* 7.1), 6.80–7.63 (9H, m); MS: *m/z* (FAB+) 363 (M^+) (36%). Anal calcd for $C_{21}H_{21}N_3O_3$: C, 69.39; H, 5.83; N, 11.57. Found: C, 69.46; H, 5.86; N, 11.64.

Compound **7a** (0.19 g, 21%), mp 138°C (from pentane–dichloromethane); $[\alpha]_D^{25}=-574.0$ (MeOH, c=0.08); IR (Nujol): 1725, 1660 (cm^{-1}); ^1H NMR δ: 1.59 (3H, d, *J* 6.9), 3.28 (1H, dd, *J* 18.1, 13.6), 3.71 (1H, d, *J* 16.6), 3.76 (3H, s), 4.18 (1H, dd, *J* 18.1, 8.5), 5.07 (1H, d, *J* 16.6), 5.65 (1H, dd, *J* 13.6, 8.5), 5.97 (1H, q, *J* 6.9), 5.99 (1H, dd, *J* 7.5, 0.7), 6.44 (1H, dt, *J* 7.5, 0.8), 7.01–7.52 (7H, m); MS: *m/z* (FAB+) 363 (M^+) (23%). Anal. calcd for $C_{21}H_{21}N_3O_3$: C, 69.39; H, 5.83; N, 11.57. Found: C, 69.41; H, 5.78; N, 11.51.

Compound **6b** (0.58 g, 61%), mp 61°C (from diisopropyl ether); $[\alpha]_D^{25}=+158.0$ (MeOH, c=0.23); IR (Nujol): 1730, 1650 (cm^{-1}); ^1H NMR δ: 1.37 (3H, d, *J* 8.0), 1.42 (3H, d, *J* 7.4), 3.78 (1H, d, *J* 17.2), 3.88

(3H, s), 4.47 (1H, dq, *J* 8.0, 6.8), 4.86 (1H, d, *J* 17.2), 5.18 (1H, d, *J* 6.8), 6.02 (1H, q, *J* 7.4), 6.85–7.65 (9H, m); MS: *m/z* (FAB+) 377 (M^+) (40%). Anal. calcd for $C_{22}H_{23}N_3O_3$: C, 69.99; H, 6.15; N, 11.14. Found: C, 69.93; H, 6.08; N, 11.22.

Compound **7b** (0.31 g, 33%), mp 165°C (from diisopropyl ether); $[\alpha]_D^{25}=-580.0$ (MeOH, c=0.20); IR (Nujol): 1700, 1660 (cm^{-1}); ^1H NMR δ: 1.40 (3H, d, *J* 7.0), 1.59 (3H, d, *J* 5.5), 3.72 (1H, d, *J* 16.6), 3.88 (3H, s), 4.47 (1H, dq, *J* 6.8, 5.5), 5.03 (1H, d, *J* 16.6), 5.18 (1H, d, *J* 6.8), 5.93 (1H, q, *J* 7.0), 5.99 (1H, dd, *J* 7.6, 0.9), 6.47 (1H, dt, *J* 7.6, 0.9), 7.05–7.52 (7H, m); MS: *m/z* (FAB+) 377 (M^+) (73%). Anal. calcd for $C_{22}H_{23}N_3O_3$: C, 69.99; H, 6.15; N, 11.14. Found: C, 69.95; H, 6.20; N, 11.20.

Compound **6c** (0.76 g, 69%), mp 204°C (from hexane–benzene); $[\alpha]_D^{25}=+374.0$ (MeOH, c=0.12); IR (Nujol): 1710, 1660 (cm^{-1}); ^1H NMR δ: 1.40 (3H, d, *J* 7.1), 3.75 (1H, d, *J* 17.4), 3.78 (3H, s), 4.82 (1H, d, *J* 17.4), 5.56 (1H, d, *J* 6.3), 5.67 (1H, d, *J* 6.3), 6.10 (1H, q, *J* 7.1), 6.90–7.80 (14H, m); MS: *m/z* (FAB+) 439 (M^+) (49%). Anal. calcd for $C_{27}H_{25}N_3O_3$: C, 73.77; H, 5.74; N, 9.57. Found: C, 73.83; H, 5.80 N, 9.66.

Compound **7c** (0.30 g, 27%), mp 232°C (from hexane–benzene); $[\alpha]_D^{25}=-766.0$ (MeOH, c=0.04); IR (Nujol): 1710, 1660 (cm^{-1}); ^1H NMR δ: 1.54 (3H, d, *J* 7.0), 3.73 (1H, d, *J* 16.8), 3.78 (3H, s), 5.03 (1H, d, *J* 16.8), 5.52 (1H, d, *J* 6.5), 5.61 (1H, d, *J* 6.5), 6.06 (1H, q, *J* 7.0), 6.11 (1H, dd, *J* 7.4, 1.0), 6.52 (1H, dt, *J* 7.4, 0.8), 7.15–7.70 (12H, m); MS: *m/z* (FAB+) 439 (M^+) (65%). Anal. calcd for $C_{27}H_{25}N_3O_3$: C, 73.77; H, 5.74; N, 9.57. Found: C, 73.72; H, 5.70; N, 9.60.

*3.6. X-Ray structure determination of **7a**, **7b** and **7c***

Crystal data were collected with a Bruker P4 diffractometer, using graphite monochromated Mo-$K\alpha$ radiation λ=0.71073 Å. The structures were solved by SIR92,[12] and refined on F^2 by full-matrix least-squares using SHELX97;[13] heavy atoms were anisotropic, H atoms isotropic. Absolute configurations were based on the reactants knowledge.

Data of **7a**. $C_{21}H_{21}N_3O_3$, M_r=363.41, triclinic, *a*=7.1179(4), *b*=7.8192(5), *c*=8.7364(5) Å, α=83.763(6), β=76.012(5), γ=82.907(6)°, *V*=466.64(5) $Å^3$, space group *P*1, *T*=291(1) K, *Z*=1, d_{calc}=1.293 g cm^{-1}, μ(Mo-*K*α)=0.088 mm^{-1}; $\omega/2\theta$ scans, $4<2\theta<60°$; $-9<h<0$, $-10<k<10$, $-12<l<11$; 2893 unique reflections collected; used for all calculations. Final *R*=0.0341 and *wR*=0.0942, g.o.f. 1.045, $-0.11<\Delta\rho<0.14$ e$Å^{-3}$.

Data of **7b**. $C_{22}H_{23}N_3O_3$, M_r=377.43, tetragonal, *a*=9.7685(7), *c*=21.0340(18) Å, *V*=2007.1(3) $Å^3$, space group $P4_1$, *T*=291(1) K, *Z*=4, d_{calc}=1.249 g cm^{-1}, μ(Mo-*K*α)=0.084 mm^{-1}; $\omega/2\theta$ scans, $4<2\theta<55°$; $-1<h<12$, $0<k<12$, $-27<l<27$; 5844 reflections collected, 4604 unique (R_{int}=0.0156) used for all calculations. Final *R*=0.0635 and *wR*=0.0822, g.o.f. 1.031; $-0.09<\Delta\rho<0.09$ e$Å^{-3}$.

Data of **7c**. $C_{27}H_{25}N_3O_3$, M_r=439.50, monoclinic, *a*=9.5131(8), *b*=9.8418(10), *c*=12.3063(13) Å, β=99.242(7)°, *V*=1137.9(2) $Å^3$, space group $P2_1$, *T*=291(1) K, *Z*=2, d_{calc}=1.283 g cm^{-1}, μ(Mo-*K*α)=0.085 mm^{-1}; $\omega/2\theta$ scans, $4<2\theta<55°$; $-1<h<12$, $-1<k<12$, $-15<l<15$; 3605 reflections collected, 3077 unique (R_{int}=0.0258) used for all calculations. Final *R*=0.0415 and *wR*=0.0739, g.o.f. 1.012, $-0.11<\Delta\rho<0.14$ e$Å^{-3}$.

Bond distances and bond angles are in the expected range for all three molecules. These compounds differ mainly because the N2=C3–C5=O18 system is *cis* in **7a** and *trans* in **7b** and **7c**. Also, the ring N1, N2, C3, C4, C5 is quite different, being about planar in **7a**, while **7b** shows a twisted conformation [$4T_5$, q_2=0.131(2) Å, $\varphi_2=-48.8(8)°$][14] and **7c** has the opposite one [$5T_4$, q_2=0.100(2) Å, φ_2=132.1(10)°]. On the contrary, the seven-membered ring has about the same conformation in all molecules.

Acknowledgements

We are grateful to CNR and MURST for financial support.

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