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Stereoselective intramolecular cycloadditions of homochiral *N*-alkenoyl aryl azides

Gianluigi Broggini,[b] Luisa Garanti,[a,*] Giorgio Molteni[a] and Tullio Pilati[c]

[a]*Dipartimento di Chimica Organica e Industriale, Università di Milano, via Golgi 19, 20133 Milan, Italy*
[b]*Dipartimento di Scienze Chimiche, Fisiche e Matematiche, Università dell'Insubria, via Lucini 3, 22100 Como, Italy*
[c]*Consiglio Nazionale delle Ricerche, Centro per lo Studio delle Relazioni tra Struttura e Reattività Chimica, via Golgi 19, 20133 Milan, Italy*

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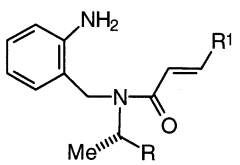
Abstract—Starting from the commercially available (*S*)-1-phenylethylamine and L-alanine benzylester, we synthesised the homochiral *N*-alkenoyl aryl azides **2a**–**2d**. The intramolecular cycloaddition of unsubstituted **2a** and **2b** gave enantiopure 3,3a-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones **3a**, **3b**, **4a** and **4b**, while phenyl-substituted **2c** and **2d** gave enantiopure 1,1a-dihydro-2*H*-azirino[2,1-*c*][1,4]benzodiazepine-4(6*H*)-ones **5c**, **5d**, **6c** and **6d**.

1. Introduction

Stereoselective 1,3-dipolar cycloaddition methodology[1] represents one of the most fruitful fields within contemporary organic chemistry. In recent years, the cycloaddition approach has allowed many successful syntheses of enantiomerically pure molecules, which would be difficult to obtain by different routes. There are many examples in which the stereoselective intramolecular cycloaddition of chiral azides plays a key role in the construction of valuable synthetic targets. Among them, pyrrolizidine and indolizidine alkaloids,[2] amaryllidaceae alkaloids[3] and biotin[4] are of particular note. However, all of these synthetic approaches rely on the spontaneous degradation of the first-formed 4,5-dihydro-1,2,3-triazole ring, which has very low stability under the cycloaddition conditions. We present here the first stereoselective synthesis of enantiopure 3,3a-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones **3a**, **3b**, **4a** and **4b** and 1,1a-dihydro-2*H*-azirino[2,1-



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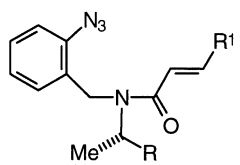

2

Entry	a	b	c	d
R^1	H	H	Ph	Ph
R	Ph	$COOCH_2Ph$	Ph	$COOCH_2Ph$

Figure 1.

* Corresponding author.

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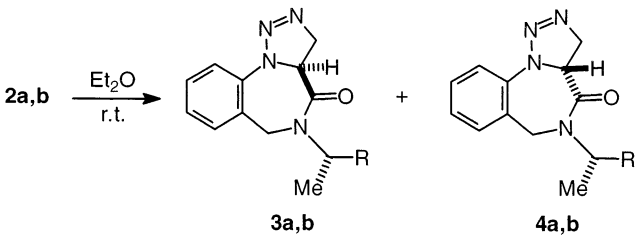
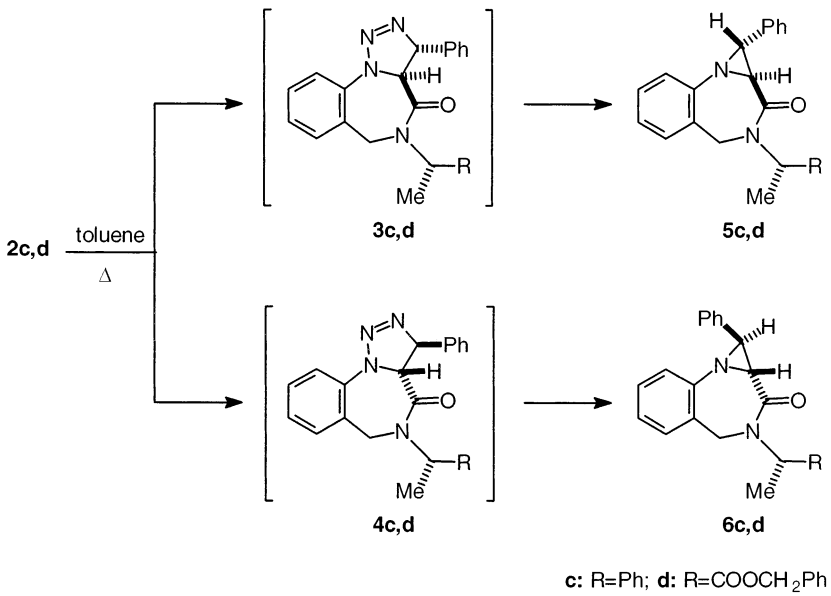


Scheme 1.

c][1,4]benzodiazepine-4(6*H*)-ones **5c**, **5d**, **6c** and **6d** from the intramolecular cycloaddition of homochiral *N*-alkenoyl aryl azides **2**. The inexpensive, commercially available (*S*)-1-phenylethylamine and L-alanine benzylester were used as the starting chiral units.

2. Results and discussion

N-[(*S*)-1-Phenylethyl]-2-aminobenzylamines **1a** and **1b**[5] and the benzyl *N*-[(2-aminophenyl) methylene]-L-alaninates **1c** and **1d**[6] were synthesised as recently reported by us. Diazotisation of the latter followed by treatment with sodium azide gave the desired *N*-alkenoyl aryl azides **2** with good yields (Fig. 1). Unsubstituted **2a** and **2b** were not fully characterised because of their lability even at room temperature. In fact, the latter partially underwent spontaneous intramolecular cycloaddition to the diastereoisomeric 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepinones **3a**, **4a** and **3b**, **4b**, respectively, during the reaction workup. The complete conversion of **2a** and **2b** to the cycloadducts was achieved by stirring a 0.02 M ethereal solution of the crude azides at room temperature (Scheme 1). By contrast, phenyl-substituted azides **2c** and **2d**, being far more stable than **2a** and **2b**, were obtained as crystalline solids and could be fully characterised. Compounds **2c** and **2d**, which were proven to be stable under the above reaction conditions, were further reacted in refluxing toluene in the presence of 1% triethylamine giving the diastereoisomeric aziridino-[2,1-*c*][1,4]benzodiazepinones **5c**–**6c** and **5d**–**6d**, respectively (Scheme 2). Products and their isolated yields, as well as reaction times and chromatography eluents, are collected in Table 1. The overall yields of the intramolecular cycloaddition reactions were consistently good. Furthermore, simple silica gel chromatography of the crude products allowed the clean separa-

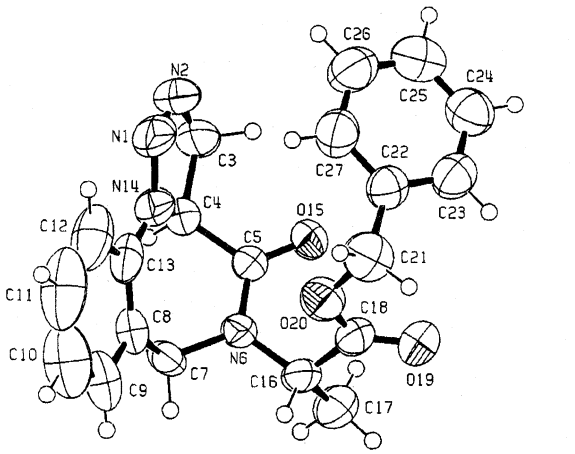


Scheme 2.

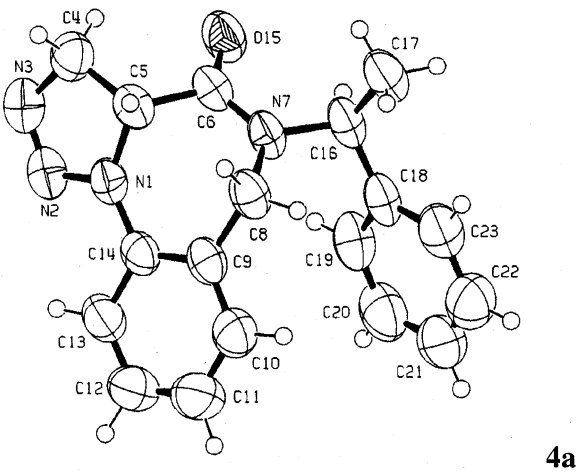
Table 1. Intramolecular cycloadditions of *N*-alkenoyl aryl azides **2**

Compd	Time (h)	Products and yields[c]				Eluent[d]
		3	**4**	**5**	**6**	
2a	0.75[a]	61	28	–	–	Et_2O–LP (2:1)
2b	0.5[a]	57	18	–	–	Et_2O
2c	7.5[b]	–	–	58	33	Et_2O
2d	6.5[b]	–	–	47	31	AcOEt–hexane (1:1)

[a] In dry Et_2O, rt.
[b] In refluxing toluene.
[c] Isolation yields.
[d] LP = light petroleum, bp 40–60°C.



3b



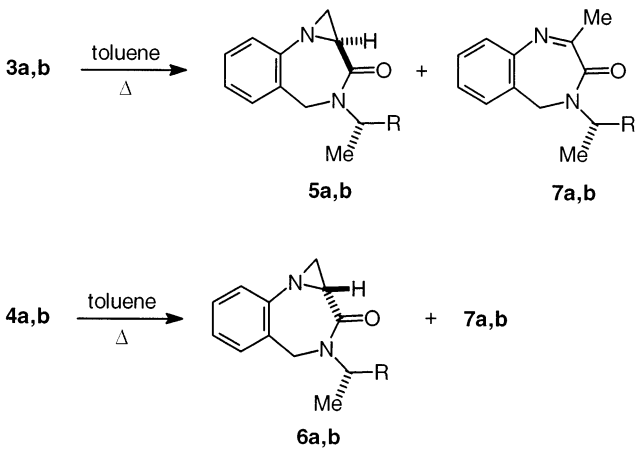
4a

Figure 2. ORTEP plots of **3b** (structure A, see Section 3.5) and **4a** (structure B, see Section 3.5) with the crystallographic numbering scheme. Ellipsoids at 50% probability level. H atoms not to scale.

tion of the diastereoisomeric products **3**, **4**, **5** and **6** in pure form. Basic reaction media and eluents were needed because of the known lability of compounds such as **5** or **6** towards acidic species.[7] Structural assignment of the above products relied upon analytical and spectral data. In the case of minor diastereoisomer **4a**, the ^{1}H NMR spectra show resonance of the C(7) and C(8) aromatic hydrogens at $\delta = 6.03$ and 6.51, respectively. These upfield shifted values can only be justified by invoking a shielding effect from the phenyl ring of the (*S*)-1-phenylethyl pendant. This shielding effect, which is absent in the case of major diastereoisomer **3a**, can only be operative if the triazoline C-(5) has (*R*)-absolute configuration, in close analogy with the structurally related pyrazolo[1,5-*a*][1,4]benzodiazepine-4-(6*H*)-ones, as recently proposed by us.[5] On the basis of the same considerations one can attribute the absolute configuration of the aziridinic C-(3) of **5c** and **6c**. Here again, a strong shielding effect causes upfielded resonances (C(7)H, $\delta = 5.60$ and C(8)H, $\delta = 6.40$) in the case of the minor diastereoisomer **6c**, thus suggesting the (*R*)-configuration at C(3), while the lack of the shield for the major diastereoisomer **5c** may be indicative of (*S*)-configuration. Furthermore, the coupling constants found for the protons of the aziridine ring of **5c** and **6c** (3.2–3.5 Hz) agree with those reported for similar nitrogen bridgehead aziridines[8] and indicate a *trans*-arrangement of these protons, thus accounting for the depicted (1a*S*,2*R*)-configuration of **5c** and the (1a*R*,2*R*)-configuration of **6c**. The X-ray diffraction analysis of minor diastereoisomer **4a** (Fig. 2) fully supported the above assignments, and consequently the (*S*)-absolute configuration can be assigned to the major cycloadduct **3a**. Unfortunately, the ^{1}H NMR spectra of cycloadducts **3b** and **4b** were very similar to each other and lacked any shielding effect due to the L-alanine benzylester pendant. The (*S*)-absolute configuration to the triazoline C(5) of the major diastereoisomer **3b** was elucidated by X-ray diffraction analysis, but the absolute configuration of the aziridine C(3) of **5d** and **6d** could only be tentatively assigned. In this respect, it can be assumed that the transition states leading to the major triazolines **3b** and **3d** are configurationally similar, thus accounting for the (*S*)-configuration of the newly formed stereocentres in both **3b** and **5d**.

As can be seen in Table 1, intramolecular cycloadditions of azides **2** show stereoselectivities ranging from fair to good; the ratios 3/4 and 5/6 encompass the range from 60:40 (Table 1, **2d**) to 73:27 (Table 1, **2b**). This result is noteworthy considering the large distance between the pre-existing and the newly-formed stereocentres.

The stability of **3a**, **3b**, **4a** and **4b** is somewhat surprising in the light of the known thermal lability of Δ^2-1,2,3-triazolines,[9] whose decomposition leads to aziridines or imine derivatives. However, intramolecular cycloaddition of **2a** and **2b** occurs at room temperature, thus allowing the isolation of pure **3a**, **3b**, **4a** and **4b** from the diastereomeric mixtures in good overall yields. Similar tricyclic structures **3c** and **3d**, which are involved in the thermal decomposition of phenyl-substituted azides **2c** and **2d**, undergo loss of nitrogen to give



a: R = Ph, **b:** R = $COOCH_2Ph$

Scheme 3.

Table 2. Thermal behaviour of 1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones **3** and **4**

Compd	Time (h)[a]	Products and yields[b]						Eluent[c]
		5a	**5b**	**6a**	**6b**	**7a**	**7b**	
3a	1	43	–	–	–	44	–	AcOEt–CH_2Cl_2 (1:1)
3b	1	–	48	–	–	44	–	AcOEt–LP (1:1)
4a	6	–	–	30	–	–	42	Et_2O
4b	8	–	–	–	53	–	43	Et_2O

[a] In refluxing toluene.
[b] Isolation yields.
[c] LP = light petroleum, bp 40–60°C.

the aziridines **5c**, **5d**, **6c** and **6d**. The lack of imine derivatives when starting from azides **2c** and **2d** may be attributed to the stabilizing effect of the phenyl group on the adjacent electron-deficient carbon atom. This picture is substantiated by thermal decomposition of the triazolinic cycloadducts **3a**, **3b**, **4a** and **4b**, which was carried out in refluxing toluene and gave a mixture of enantiopure aziridines **5a** and **6a** and imines **7a** and **7b** (Table 2 and Scheme 3). It should be added that the absence of geminal coupling in the case of **5a** and **6a** parallels those observed for similar nitrogen bridgehead aziridines.[7,10]

In conclusion, the course of the intramolecular cycloadditions of azides **2a**–**2d** is strongly influenced by both the reaction conditions and R^1. Moreover, direct intramolecular azide cycloaddition allowed the first successful synthesis of enantiopure compounds **3**–**7** of potential pharmacological interest.

3. Experimental

Melting points were determined with a Büchi apparatus in open tubes 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 at room temperature unless otherwise stated). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. Optical rotations, $[\alpha]_D^{25}$, were recorded on a Perkin–Elmer Model 241 polarimeter at the sodium D line.

Because of the large overlapping of the signals, ^{1}H NMR spectra of compounds **7a** and **7b** were taken in $CDCl_3$ solutions at 60°C.

3.1. General procedure for the synthesis of *N*-alkenoyl aryl azides 2

A solution of **1** (10.0 mmol) in aqueous hydrochloric acid (6 M, 8.0 mL) and acetic acid (4.0 mL) was treated with sodium nitrite (1.04 g, 15.0 mmol) under stirring and cooling at 0°C. After 30 min, the mixture was treated with cold diethyl ether (25 mL) and sodium azide (3.22 g, 0.05 mol) was added portionwise under vigorous stirring and ice-cooling. After 1 h, the organic layer was separated, washed with 5% aqueous sodium hydrogen carbonate (30 mL), then with water (50 mL), and dried over sodium sulfate. Evaporation of the solvent gave crude **2a**–**2d** as brown oily residues.

Compounds **2a** and **2b** were used without further purification. **2a** (2.94 g, 96%) IR (neat): 2120, 1660 (cm^{-1}); **2b** (3.57 g, 98%) IR (neat): 2130, 1650 (cm^{-1}).

In the remaining cases, the residue was chromatographed on a silica gel column with hexane–AcOEt (2:1) as eluent giving **2c** and **2d**.

2c (3.29 g, 86%), mp 95–97°C, as a pale yellow solid (from di-*iso*-propyl ether); $[\alpha]_D^{25} = -19.6$ ($CHCl_3$, $c = 0.20$); IR (Nujol): 2125, 1640 (cm^{-1}); ^{1}H NMR δ: 1.50 (3H, d, $J = 8.1$), 4.30 (1H, d, $J = 19.0$), 4.47 (1H, d, $J = 19.0$), 6.27 (1H, q, $J = 8.1$), 6.55 (1H, d, $J = 15.3$), 6.90–7.50 (14H, m), 7.80 (1H, d, $J = 15.3$); MS *m*/*z* 382 (M^+) (44%). Anal. calcd for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80; N, 14.65. Found: C, 75.46; H, 5.86; N, 14.58%.

2d (3.92 g, 89%), mp 75–76°C, as a pale yellow solid (from di-*iso*-propyl ether); $[\alpha]_D^{25} = +7.1$ ($CHCl_3$, $c = 1.82$); IR (Nujol): 2125, 1740, 1640 (cm^{-1}); ^{1}H NMR δ: 1.48 (3H, d, $J = 7.8$), 4.27 (1H, d, $J = 19.0$), 4.55 (1H, d, $J = 19.0$), 4.73 (1H, d, $J = 17.4$), 4.90 (1H, d, $J = 17.4$), 5.16 (1H, q, $J = 7.8$), 6.60 (1H, d, $J = 15.7$), 6.90–7.50 (14H, m), 7.75 (1H, d, $J = 15.7$); MS *m*/*z* 440 (M^+) (31%). Anal. calcd for $C_{26}H_{24}N_4O_2$: C, 70.89; H, 5.49; N, 12.72. Found: C, 70.95; H, 5.46; N, 12.80%.

3.2. 3,3a-Dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones 3 and 4

A solution of **2a** and **2b** (9.0 mmol) in dry diethyl ether (450 mL) was stirred at room temperature for the time indicated in Table 1. Evaporation of the solvent gave a residue that was chromatographed on a silica gel column with the eluent given in Table 1. The major diastereoisomers **3** were eluted first, followed by minor diastereoisomers **4**.

3a (1.68 g, 61%), mp 126–128°C, as a colourless solid (from di-*iso*-propyl ether); $[\alpha]_D^{25} = +73.6$ ($CHCl_3$, $c = 0.24$); IR (Nujol): 1660 (cm^{-1}); ^{1}H NMR δ: 1.42 (3H, d, $J = 7.9$), 3.78 (1H, d, $J = 16.7$), 4.55 (1H, dd, $J = 18.1$, 14.0), 4.94 (1H, d, $J = 16.7$), 5.15 (1H, dd, $J = 14.0$,

10.6), 5.40 (1H, dd, $J=18.1$, 10.6), 6.05 (1H, q, $J=7.9$), 6.90–7.90 (9H, m); MS m/z 306 (M^+) (75%). Anal. calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.65; H, 5.99; N, 18.19%.

4a (0.77 g, 28%), mp 106–107°C, as a colourless solid (from di-*iso*-propyl ether); $[\alpha]_D^{25}=-330.9$ ($CHCl_3$, $c=0.28$); IR (Nujol): 1660 (cm^{-1}); ^1H NMR δ: 1.55 (3H, d, $J=7.8$), 3.75 (1H, d, $J=17.0$), 4.55 (1H, dd, $J=18.5$, 12.5), 5.06 (1H, d, $J=17.0$), 5.15 (1H, dd, $J=12.5$, 9.2), 5.38 (1H, dd, $J=18.5$, 9.2), 5.95 (1H, q, $J=7.8$), 6.03 (1H, dd, $J=7.2$, 1.6), 6.51 (1H, dt, $J=7.3$, 1.8), 7.20–7.72 (7H, m); MS m/z 306 (M^+) (59%). Anal. calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.60; H, 5.94; N, 18.34%.

3b (1.87 g, 57%), mp 94–96°C, as a colourless solid (from di-*iso*-propyl ether); $[\alpha]_D^{25}=+106.9$ ($CHCl_3$, $c=0.28$); IR (Nujol): 1740, 1670 (cm^{-1}); ^1H NMR δ: 1.42 (3H, d, $J=8.0$), 4.00 (1H, d, $J=17.0$), 4.52 (1H, dd, $J=18.0$, 12.0), 5.16 (2H, s), 5.20–5.30 (4H, m), 6.90–7.80 (9H, m); MS m/z 364 (M^+) (36%). Anal. calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.88; H, 5.60; N, 15.44%.

4b (0.59 g, 18%), mp 88–90°C, as a colourless solid (from di-*iso*-propyl ether); $[\alpha]_D^{25}=-122.0$ ($CHCl_3$, $c=0.21$); IR (Nujol): 1740, 1660 (cm^{-1}); ^1H NMR δ: 1.45 (3H, d, $J=8.0$), 4.00 (1H, d, $J=17.0$), 4.49 (1H, dd, $J=18.2$, 12.0), 4.53 (1H, d, $J=11.8$), 4.93 (1H, dd, $J=11.8$), 5.12–5.30 (4H, m), 6.90–7.80 (9H, m); MS m/z 364 (M^+) (44%). Anal. calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.99; H, 5.50; N, 15.31%.

3.3. 1,1a-Dihydro-2-phenyl-2*H*-azirino[2,1-*c*][1,4]benzodiazepine-4(6*H*)-ones 5c, 5d, 6c and 6d

A solution of **2c**, **2d** (9.0 mmol) and triethylamine (3.90 g, 38.6 mmol) in dry toluene (450 mL) was refluxed for the time indicated in Table 1. Evaporation of the solvent gave a residue that was chromatographed on a silica gel column with the eluent given in Table 1. Major diastereoisomers **5c** and **5d** were eluted first, followed by minor diastereoisomers **6c** and **6d**.

5c (1.85 g, 58%), mp 68–70°C, as a colourless solid (from di-*iso*-propyl ether); $[\alpha]_D^{25}=-79.2$ ($CHCl_3$, $c=0.26$); IR (Nujol): 1650 (cm^{-1}); ^1H NMR δ: 1.45 (3H, d, $J=7.9$), 3.32 (1H, d, $J=3.1$), 3.39 (1H, d, $J=3.1$), 3.64 (1H, d, $J=14.7$), 4.78 (1H, d, $J=14.7$), 6.02 (1H, q, $J=7.9$), 6.90–7.40 (14H, m); MS m/z 354 (M^+) (49%). Anal. calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.40; H, 6.32; N, 7.97%.

6c (1.05 g, 33%) as a pale yellow oil; $[\alpha]_D^{25}=+46.7$ ($CHCl_3$, $c=0.15$); IR (neat): 1640 (cm^{-1}); ^1H NMR δ: 1.61 (3H, d, $J=7.9$), 3.31 (1H, d, $J=3.3$), 3.37 (1H, d, $J=3.3$), 3.64 (1H, d, $J=14.9$), 4.89 (1H, d, $J=14.9$), 5.67 (1H, dd, $J=7.4$, 1.8), 6.07 (1H, q, $J=7.9$), 6.42 (1H, dt, $J=7.8$, 1.5), 6.90–7.60 (12H, m); MS m/z 354 (M^+) (59%).

5d (1.74 g, 47%) as a colourless oil; $[\alpha]_D^{25}=-47.7$ ($CHCl_3$, $c=0.40$); IR (Nujol): 1740, 1650 (cm^{-1}); ^1H NMR δ: 1.39 (3H, d, $J=7.6$), 3.21 (1H, d, $J=3.5$), 3.35 (1H, d, $J=3.5$), 3.87 (1H, d, $J=15.5$), 5.12 (1H, d, $J=15.5$), 5.17 (1H, d, $J=12.8$), 5.22 (1H, d, $J=12.8$), 5.43 (1H, q, $J=7.6$), 6.80–7.50 (14H, m); MS m/z 412 (M^+) (63%).

6d (1.15 g, 31%) as a pale yellow oil; $[\alpha]_D^{25}=+83.7$ ($CHCl_3$, $c=0.27$); IR (neat): 1740, 1650 (cm^{-1}); ^1H NMR δ: 1.49 (3H, d, $J=7.9$), 3.18 (1H, d, $J=3.2$), 3.31 (1H, d, $J=3.2$), 3.92 (1H, d, $J=15.5$), 4.60 (1H, d, $J=12.6$), 5.02 (1H, d, $J=12.6$), 5.12 (1H, d, $J=15.5$), 5.26 (1H, q, $J=7.9$), 6.60–7.50 (14H, m); MS m/z 412 (M^+) (34%).

3.4. Thermal behaviour of 1,2,3-triazoles 3a, 3b, 4a and 4b

A solution of **3a**,**b** or **4a**,**b** (5.0 mmol) and triethylamine (2.20 g, 21.8 mmol) in dry toluene (250 mL) was refluxed for the time indicated in Table 2. Evaporation of the solvent gave a residue that was chromatographed on a silica gel column with the eluent given in Table 2. Imines **7a** or **7b** were eluted first, followed by aziridines **5a** and **5b** or **6a** and **6b**, respectively.

7a as a colourless oil; $[\alpha]_D^{25}=+120.0$ ($CHCl_3$, $c=0.20$); IR (neat): 1630 (cm^{-1}); ^1H NMR δ: 1.45 (3H, d, $J=7.7$), 2.60 (3H, s), 3.70 (2H, s), 5.85 (1H, q, $J=7.7$), 6.80–7.40 (9H, m); MS m/z 278 (M^+) (74%).

5a (0.60 g, 43%) as a colourless oil; $[\alpha]_D^{25}=+96.2$ ($CHCl_3$, $c=0.28$); IR (neat): 1650 (cm^{-1}); ^1H NMR δ: 1.40 (3H, d, $J=7.1$), 2.13 (1H, d, $J=3.7$), 2.70 (1H, d, $J=5.9$), 3.30 (1H, dd, $J=5.9$, 3.7), 3.60 (1H, d, $J=14.7$), 4.75 (1H, d, $J=14.7$), 6.00 (1H, q, $J=7.1$), 7.10–7.40 (9H, m); MS m/z 278 (M^+) (29%).

6a (0.42 g, 30%) as a colourless oil; $[\alpha]_D^{25}=-256.4$ ($CHCl_3$, $c=0.36$); IR (neat): 1650 (cm^{-1}); ^1H NMR δ: 1.59 (3H, d, $J=7.6$), 2.10 (1H, d, $J=4.0$), 2.70 (1H, d, $J=5.8$), 3.27 (1H, dd, $J=5.8$, 4.0), 3.60 (1H, d, $J=15.0$), 4.85 (1H, d, $J=15.0$), 5.60 (1H, dd, $J=7.6$, 1.1), 6.03 (1H, q, $J=7.6$), 6.40 (1H, dt, $J=7.5$, 1.2), 6.90–7.30 (7H, m); MS m/z 278 (M^+) (36%).

7b as a colourless oil; $[\alpha]_D^{25}=+204.8$ ($CHCl_3$, $c=0.27$); IR (neat): 1740, 1650 (cm^{-1}); ^1H NMR δ: 1.42 (3H, d, $J=7.9$), 2.55 (3H, s), 4.12 (2H, s), 5.18 (2H, s), 5.29 (1H, q, $J=7.9$), 7.10–7.40 (9H, m); MS m/z 336 (M^+) (89%).

5b (0.81 g, 48%) as a colourless oil; $[\alpha]_D^{25}=+67.6$ ($CHCl_3$, $c=0.19$); IR (neat): 1740, 1650 (cm^{-1}); ^1H NMR δ: 1.38 (3H, d, $J=7.6$), 2.05 (1H, d, $J=3.7$), 2.68 (1H, d, $J=5.5$), 3.28 (1H, dd, $J=5.5$, 3.7), 3.83 (1H, d, $J=15.8$), 5.10–5.23 (3H, m), 5.37 (1H, q, $J=7.6$), 6.80–7.40 (9H, m); MS m/z 336 (M^+) (48%).

6b (0.89 g, 53%) as a colourless oil; $[\alpha]_D^{25}=-83.8$ ($CHCl_3$, $c=0.28$); IR (neat): 1740, 1650 (cm^{-1}); ^1H NMR δ: 1.45 (3H, d, $J=7.5$), 2.03 (1H, d, $J=3.7$), 2.68

(1H, d, $J=5.7$), 3.24 (1H, dd, $J=5.7$, 3.7), 3.88 (1H, d, $J=16.0$), 4.57 (1H, d, $J=12.7$), 4.9 (1H, d, $J=12.7$), 5.08 (1H, d, $J=16.0$), 5.23 (1H, q, $J=7.5$), 6.80–7.25 (9H, m); MS m/z 336 (M^+) (51%).

3.5. Crystal data for compounds 3b and 4a

3b: $C_{20}H_{20}N_4O_3$, Fw = 364.40, triclinic, space group $P\bar{1}$, $a=8.5433(8)$ Å, $b=11.1139(11)$ Å, $c=11.1251(12)$ Å, $\alpha=72.371(7)°$, $\beta=69.721(6)°$, $\gamma=89.073(7)°$, $V=939.6(2)$ Å^3, $Z=2$, $D_x=1.288$ Mg m^{-3}, μ(Mo Kα) = 0.089 mm^{-1}; crystal dimensions 0.60×0.36×0.16 mm^3, $\lambda=0.71073$ Å (Mo Kα radiation, graphite monochromator, Bruker P4 diffractometer). Data collection at 291 K, ω–2θ scan mode, $4<2\theta<55°$, h 0→11, k −13→14, l −13→14; 4989 collected reflections, 4252 unique [3122 with $I_o>2\sigma(I_o)$], merging $R=0.0179$. The structure was solved by SIR-92[11] and refined by SHELXL-97[12] by full-matrix least-squares based on F_o^2, with weights $w=1/[\sigma^2(F_o)^2+(0.0410P)^2]$, where $P=(F_o^2+2F_c^2)/3$. H atoms of benzyl, phenyl and methyl groups were calculated (riding model). The final consistency indexes were $R=0.0573$ and $R_w=0.0896$ (0.0378 and 0.0821, respectively, for observed reflections), goodness-of-fit = 1.011. The final map ranges between −0.10 and 0.11 e Å^{-3}. The absolute configuration was determined on the basis of the known configuration of L-alanine benzylester. The two independent molecules (with the same numbering scheme but signed as A and B, respectively) have similar geometrical parameters. The main differences are on the conformation of the seven-membered ring: here the torsion angles C(8)–C(13)–N(14)–C(4) and N(6)–C(7)–C(8)–C(9) measure 10.3(4) and −129.7(2)°, respectively, in molecule A (see Fig. 1) versus −1.3(4) and −121.2(3)° in molecule B.

4a: $C_{18}H_{18}N_4O$, Fw = 364.40, triclinic, space group $P2_1$, $a=16.0395(16)$ Å, $b=5.9632(6)$ Å, $c=17.0305(19)$ Å, $\beta=100.605(7)°$, $V=1601.1(3)$ Å^3, $Z=4$, $D_x=1.271$ Mg m^{-3}, μ(Mo Kα) = 0.082 mm^{-1}; crystal dimensions 0.54×0.31×0.20 mm^3, $\lambda=0.71073$ Å (Mo Kα radiation, graphite monochromator, Bruker P4 diffractometer). Data collection at 291 K, ω–2θ scan mode, $4<2\theta<52°$, h 0→19, k 0→7, l −21→20; 8452 collected reflections, 3474 unique [2173 with $I_o>2\sigma(I_o)$], merging $R=0.0344$. The structure was solved by SIR-92[11] and refined by SHELXL-97[12] by full-matrix least-squares based on F_o^2, with weights $w=1/[\sigma^2(F_o)^2+(0.0396P)^2]$, where $P=(F_o^2+2F_c^2)/3$. H atoms of phenyl and methyl groups were calculated (riding model). The final consistency indexes were $R=0.0618$ and $R_w=0.0768$ (0.0321 and 0.0659, respectively, for observed reflections), goodness-of-fit = 0.851. The final map ranges between −0.09 and 0.11 e Å^{-3}. The absolute configuration was determined on the basis of known configuration of (*S*)-1-phenylethylamine. The two independent molecules (with the same numbering scheme but signed as A and B, respectively) show similar geometrical parameters. The main differences are on the torsion angles around the C(16)–C(18) bond (see Fig. 1): for example the torsion N(7)–C(16)–C(18)–C(23) is −127.6(3)° for molecule A and −115.8(3)° for molecule B.

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