HETEROCYCLES, Vol. 63, No. 10, 2004, pp. 2287 - 2307
Received, 24th June, 2004, Accepted, 19th August, 2004, Published online, 20th August, 2004

NEW PREPARATIVE ROUTE TO HETARYLDIENES AND AZADIENES

Ildikó Nagy, György Hajós,* and Zsuzsanna Riedl

Chemical Research Center, Hungarian Academy of Sciences, H-1525 Budapest POBox 17, Hungary. E-mail: ghajos@chemres.hu

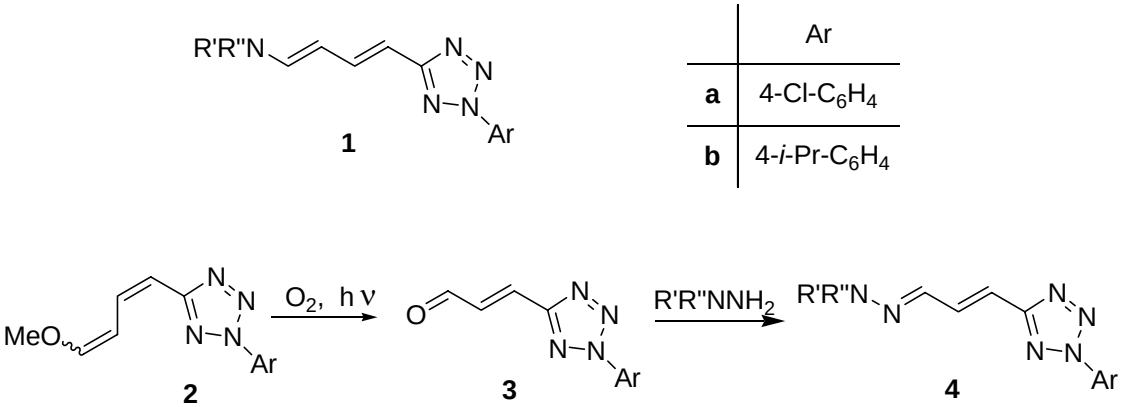
Abstract – Tetrazolylacroleins easily available *via* a four step pathway from 2-aminopyridines proved to be suitable starting compounds for preparation of new tetrazolyldiene systems. Reaction with reagents containing active methylene group gave a series of new dienes, whereas hydroxylamines yielded nitrones. The new dienes underwent cyclizations with electron withdrawn dienophiles to yield tetrazolyl substituted new polycycles, and the nitrones gave fused isoxazolines. The electron demand of the tetrazolyldienes in cycloadditions was interpreted by calculation of frontier orbital energy levels.

INTRODUCTION

In the course of our earlier investigations we have found that some hetaryldienes obtained by ring opening of tetrazolopyridinium salts by nucleophiles can serve as valuable starting materials for cyclization to new polycyclic ring systems.[1-4] For preparative reasons formation of *trans-trans* isomers was of particular importance as these compounds underwent Diels-Alder reactions as diene components.[1,5] Although we have carried out extensive research in order to elaborate further pathways to such derivatives, we had to experience, unfortunately, that the access to fully *trans*-hetaryldienes was mostly limited to dienamines (**1**).[6] We have shown that in cases when the ring opening reaction to dienes is carried out by a nucleophilic reagent different from an amine, only *cis-trans* or *cis-cis* compounds could be obtained; *e.g.* methoxydiene (**2**) was obtained as a mixture of 1-*cis*-3-*cis* and 1-*cis*-3-*trans* isomers,[6] and similar results were obtained with related alkoxy-, alkyl-, aryl-, and cyanodienes. Furthermore, all our efforts to isomerize these latter azolyldienes to a *trans-trans* derivative, most interestingly, failed.

Recently we have recognized[7] (Scheme 1) that dienyl ether (**2**) easily undergoes oxidative degradation to hetarylacroleins (**3**) (*i.e.* 1-hetaryl-4-oxadienes), and these products (**3**) can be subjected to condensation

reaction with hydrazines to yield aminoazadienes (**4**). This finding prompted us to investigate if **3** can serve as a starting compound for the synthesis of novel *trans-trans*-dienes.

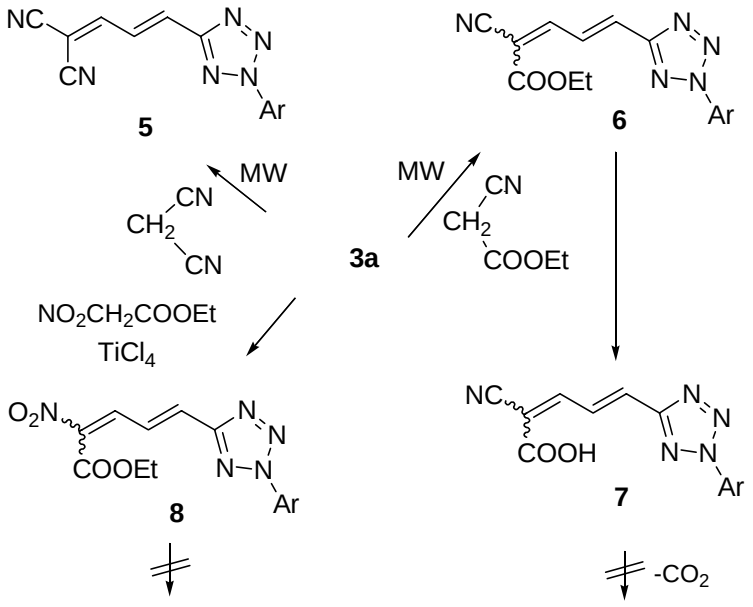


Scheme 1

In this paper we describe our efforts in this respect with particular interest to obtain new *trans-trans*-hetaryldienes containing substituents different from amines. Furthermore, reactivity of the new derivatives is also discussed.

RESULTS AND DISCUSSION

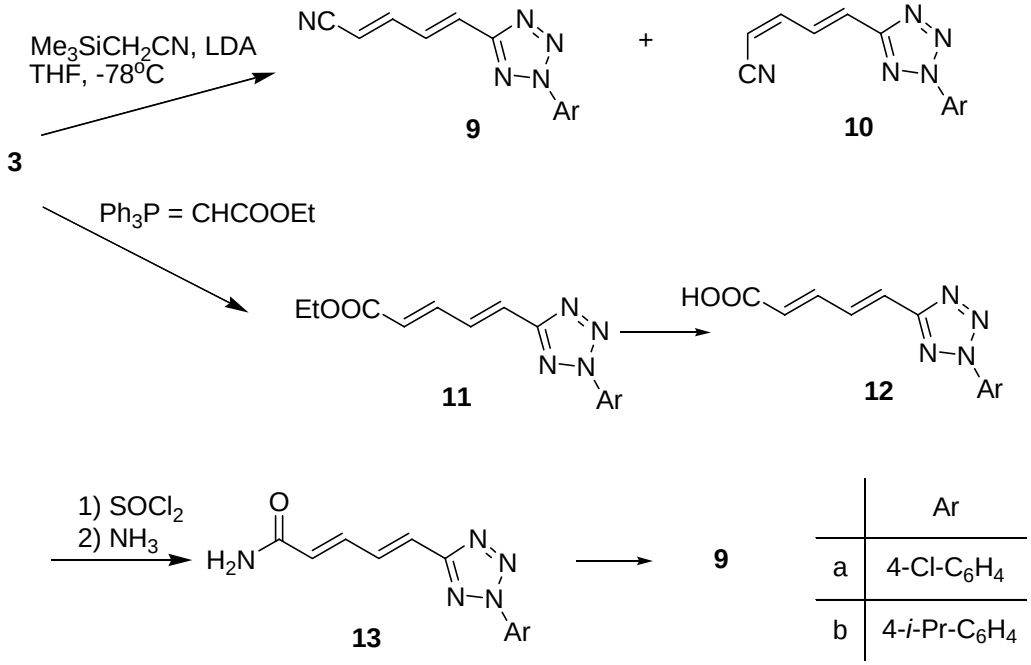
In accordance with our expectation we have found that tetrazolylacrolein (**3**) readily reacts with reagents containing active methylene groups as *C*-nucleophiles to yield dienes (Scheme 2).



Scheme 2

Some of these conversions have been carried out preferably under microwave irradiation. Thus, reaction of **3a** with malononitrile gave the 4,4-dicyano derivative (**5**), whereas cyanoacetic ester yielded the corresponding diene (**6)** bearing a cyano and an ester group in position 4. As this diene contained two substituents (an ester and a cyano group) at the terminal position of the diene chain, removal of one of them seemed desirable in order to obtain a properly substituted derivative suitable for cycloaddition. To this end, the ester group was successfully hydrolyzed to an acid (**7**). The expected decarboxylation, however, could not be realized and, thus, elaboration of a different pathway to a *trans-trans*-4-cyanodiene seemed necessary. We had to face a similar failure with reaction of **3a** with nitroacetic acid ester. Like in the previous case, the condensation reaction carried out in the presence of titanium(IV) chloride[8] took place without any difficulties to give 1-tetrazolyl-4-ethoxycarbonyl-4-nitrodiene (**8**), but all efforts for hydrolysis and decarboxylation of the ester group failed.

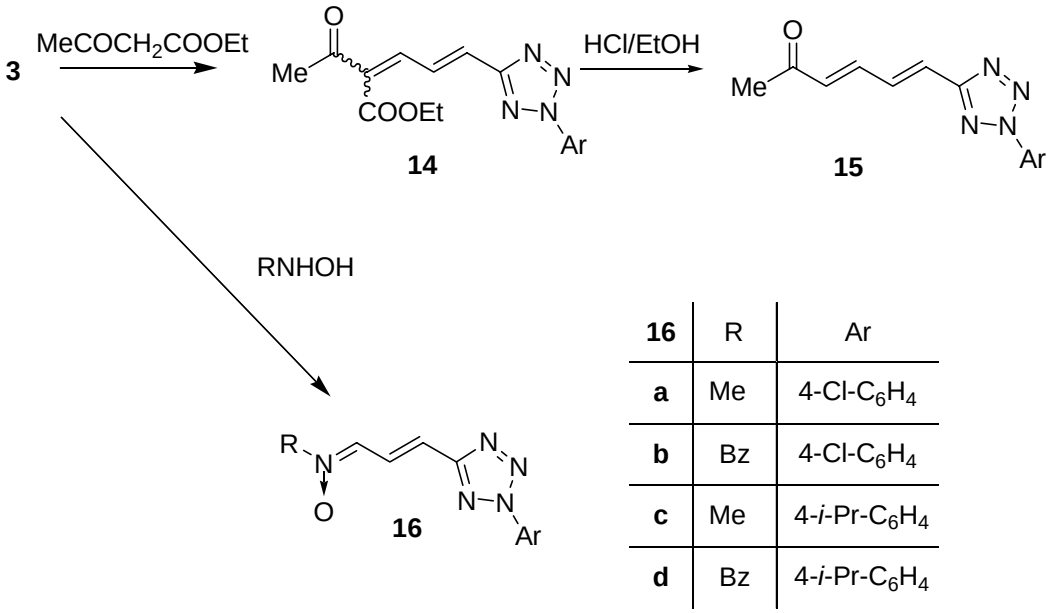
Transformation of **3** with trimethylsilylacetonitrile – a methodology published by Matsuda *et al.*[9] – proved to be more successful and resulted in a mixture of 1-*trans*-3-*trans*- and 1-*trans*-3-*cis*-1-tetrazolyl-4-cyanodienes (**9** and **10**, respectively) in a ratio of 1:1 in medium yield (Scheme 3). Although by this reaction the problem of formation of cyanodienes has been solved, its preparative importance seemed limited because of the difficulty of separation of the two isomers and failure of any experiment for isomerization of the mixture to the fully *trans* compound.



Scheme 3

A straightforward strategy for the synthesis of the *trans-trans*-diene (**9**) has, however, been found by application of Wittig reaction. Thus, reaction with ethoxycarbonyl-methylenphosphoran yielded the *trans-trans*-ester (**11**), which was easily hydrolyzed to the acid (**12**). Treatment of this compound with thionyl chloride followed by ammonia yielded the amide (**13**)**,** which was transformed by an established procedure to the 1,3-*trans-trans*-4-cyanide (**9**). This product proved to be fully identical with the sample prepared by separation of the mixture of **9** and **10** obtained from **3** as described above. We just note that a more simple procedure would have been a direct transformation of the ester (**11**) to the amide (**13**), but **11** proved to be resistant towards ammonia even under forced conditions.

Another successful transformation of **3** to a fully *trans*-tetrazolyldiene was accomplished by the reaction of ethyl acetoacetate (Scheme 4). We have found that tetrazolylacrolein (**3**) readily reacts with this reagent in the presence of a Lewis-acid (titanium(IV) chloride) and a base (*N*-methylmorpholine) to yield 4-ethoxycarbonyl-4-acetyldiene (**14**) as a mixture of stereo isomers in good yield. This compound underwent hydrolysis and subsequent decarboxylation in HCl/ethanol upon heating to give the *trans-trans*-dienyl ketone (**15**). Structure elucidation of this product by ^{1}H NMR spectrum unambiguously revealed the *trans* position of acetyl substituent at the end of the diene chain.



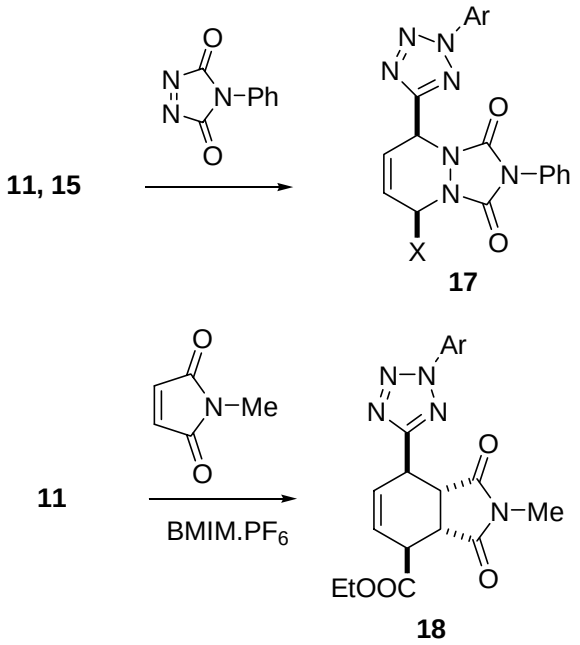
16	R	Ar
a	Me	4-Cl-C_6H_4
b	Bz	4-Cl-C_6H_4
c	Me	4-*i*-Pr-C_6H_4
d	Bz	4-*i*-Pr-C_6H_4

Scheme 4

Upon the finding[7] that tetrazolylacrolein (**3**) easily reacts with 1,1-substituted hydrazines to yield 1-azadienes (**4**) as mentioned above in the introductory part, extension of this reactivity for related reactions

seemed desirable in order to prepare azadienes as potential reaction partners for cyclizations. Thus, we have found that acrolein (**3**) reacted with substituted hydroxylamines to give nitrones (**16**) (Scheme 4).

The new *trans-trans*-dienes (**9**, **11**, **12**, **13**, **15**) and nitrones (**16**) obtained by these investigations have the common feature that they contain electron withdrawing substituents and, thus, their participance in [4+2] cycloadditions of inverse electron demand could be anticipated. In contrast to this expectation, interestingly, no such reaction was experienced (*i.e.* cycloaddition of electron donating dienophiles like cyclopentadiene, dihydrofuran, dihydropyran, ethyl vinyl ether). We have found, however, that the ester and acetyl substituted *trans-trans*-dienes (**11a,b** and **15a,b**, respectively) reacted with the strongly electron-withdrawn dienophile, *N*-phenyltriazoline dione, and yielded the regular cycloadducts (**17a-d**) (Scheme 5). Furthermore, Diels-Alder reaction of **11** with *N*-methylmaleinimide could also be carried out only in ionic liquid[10,11] to give **18a,b**.



17	X	Ar
a	MeCO	4-Cl-C_6H_4
b	COOEt	4-Cl-C_6H_4
c	MeCO	4-*i*-Pr-C_6H_4
d	COOEt	4-*i*-Pr-C_6H_4

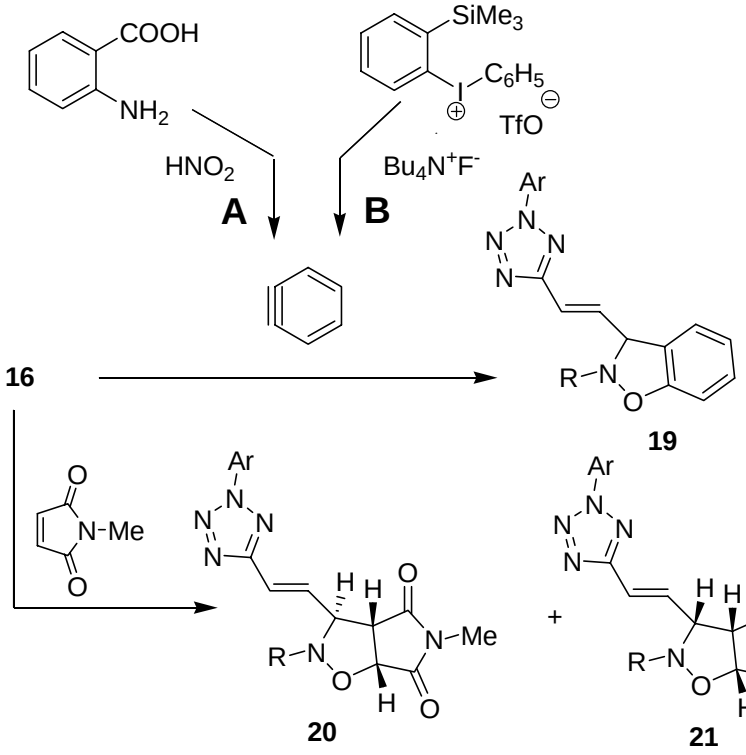
18	Ar
a	4-Cl-C_6H_4
b	4-*i*-Pr-C_6H_4

Scheme 5

In the case of nitrones (**16a,b**) some 1,3-dipolar cyclizations were also performed. Thus, reaction of **16** with benzyne gave 3-tetrazolylethenyl[1,2]benzisoxazoline (**19a-d**) (Scheme 6).

The yield was strongly dependent on the method of generation of benzyne: comparison of the yields for **19a** obtained by both method A (generation of benzyne from anthranilic acid, 40%) and method B (phenyl[2-(trimethylsilyl)phenyl]iodonium triflate,[12,13] 78%) revealed that procedure B is clearly superior

in this respect. Nitrone (**16**) also reacted with *N*-methylmaleinimide, but in this case only mixtures of stereoisomers (**20a-d**) and (**21a-d**) were obtained in a ratio of approximately 1:1.

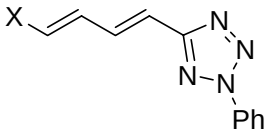


	R	Ar	method
a	Me	4-Cl-C_6H_4	A, B
b	Me	4-*i*-Pr-C_6H_4	B
c	Bz	4-Cl-C_6H_4	A
d	Bz	4-*i*-Pr-C_6H_4	B

	R	Ar
a	Me	4-Cl-C_6H_4
b	Me	4-*i*-Pr-C_6H_4
c	Bz	4-Cl-C_6H_4
d	Bz	4-*i*-Pr-C_6H_4

Scheme 6

In order to rationalize the finding that the new dienes react with electron poor dienophiles rather than with electron rich ones semiempirical calculations (PM3) have been carried out in order to analyze the orbital energies of HOMOs and LUMOs. For simplicity, the *para* substituent of the phenyl ring was replaced by a hydrogen atom. Results are shown in Table 1.



No.	X	HOMO(eV)	Δ	LUMO(eV)	Δ
1	$N(Me)_2$	-7.84		-0.82	
9	CN	-9.34	1.50	-1.43	0.61
11	COOEt	-9.26	1.42	-1.30	0.48
15	COMe	-9.29	1.45	-1.35	0.53

Table 1. Calculated HOMO and LUMO energies of differently substituted dienes

First, the HOMO and LUMO levels of dienylamine (**1**) as a control compound (a derivative found as a typical electron rich diene[6]) was calculated and, then, the same values for some new dienes bearing electron withdrawing substituents (*i.e*. **9**, **11**, **15**) were determined and the differences between these latter and the control compound were shown in separate columns (Δ values).

Comparison of these values reveals that the Δ values at the HOMOs are significantly higher than those at the LUMOs which means that replacement of the dimethylamino group with electron withdrawing substituents tremendously lowered the HOMOs, but this decrease with the LUMOs is much less and far not enough to allow these dienes to react as electron acceptor partners.

CONCLUSION

The present study led to elaboration of a facile synthetic pathway to new tetrazolyldienes that can serve as valuable starting materials in cyclizations to tetrazolyl substituted fused ring systems. The electron demand of the new dienes in Diels-Alder reactions was interpreted by theoretical considerations.

EXPERIMENTAL

Melting Points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Thermo Nicolet Avatar 320 FT-IR spectrophotometer; the NMR spectra were recorded with Varian UNITY INOVA spectrometer (200 MHz and 400 MHz for ^{1}H and 100 MHz for ^{13}C).

{(2*E*)-3-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]prop-2-en-1-ylidene}malononitrile (5)

A mixture of **3a** (0.100 g, 0.43 mmol), malononitrile (0.028 g, 0.43 mmol) and silica gel (1.5 g) was irradiated (3 x 1 min) by microwave (300 W). The product was eluated with a mixture of dichloromethane and methanol, the solvent was evaporated and the residue was treated with ether. The precipitated compound was filtered off as colorless crystals (0.068 g, 57%); **mp**: 153-155 ºC (from acetonitrile); **IR** (KBr): 3069, 3021, 2240, 1636, 1573, 1495, 1417, 1161, 1092, 995, 831 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.11-8.16 (2"+6"-H), 7.90 (dd, *J* = 12.0, 16.0 Hz, 1H), 7.75 (d, *J* = 12.0 Hz, 1H), 7.56-7.61 (3"+5"-H), 7.44 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$) δ: 162.1, 158.1, 136.8, 135.0, 132.7, 130.4, 130.2, 129.3, 121.5, 121.2; **Anal. Calcd** for $C_{13}H_7N_6Cl$: C, 55.23; H, 2.50; N, 29.73. Found: C, 55.40; H, 2.32; N, 29.42.

Ethyl (2*Z*/*E*,4*E*)-5-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]-2-cyanopenta-2,4-dienoate (6)

A mixture of **3a** (1.00 g, 4.26 mmol), ethyl cyanoacetate (0.482 g, 455 μL, 4.26 mmol) and silica gel (15 g) was irradiated (2 x 1 min) in a microwave apparatus (300 W). The product was eluated with a mixture of dichloromethane and methanol, the solvent was evaporated *in vacuo* and ether was added to the residue and

the solid product was filtered off. The title compound is a mixture of two isomers (1:1.7), colorless crystals (1.232 g, 88%); **mp**: 136-138 ºC (from 2-propanol, decomp); **IR** (KBr): 2228, 1717, 1588, 1492, 1263, 1236, 1089, 1071, 1002, 839 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.11-8.15 (2"+6"-H), 8.06 (d, *J* = 12.0 Hz, 1H), 7.89 (dd, *J* = 12.0, 16.0 Hz, 1H), 7.55-7.59 (3"+5"-H), 7.38 (d, *J* = 16.0 Hz, 1H), 4.27(4.39) (q, *J* = 6.8 Hz, 2H), 1.30(1.40) (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$) δ: 164.0, 162.7, 157.1, 153.0, 136.6, 135.3, 131.1, 130.5, 130.4, 121.5, 113.9, 63.2, 14.4; **Anal. Calcd** for $C_{15}H_{12}N_5O_2Cl$: C, 54.64; H, 3.67; N, 21.24. Found: C, 54.24; H, 3.57; N, 21.10.

(2*Z*,4*E*)-5-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]-2-cyanopenta-2,4-dienoic acid (7)

To a suspension of **6** (0.50 g, 1.52 mmol) in methanol (15 mL) was added aqueous sodium hydroxide solution (3 mL, 15 mmol, 20%) at rt and the mixture was stirred for 1 h. The solvent was removed *in vacuo*, and water (20 mL) was added to the residue and it was cooled down by ice and acidified with concentrated HCl to pH=3. The precipitated product was filtered off and washed several times with water to give colorless crystals (0.452 g, 99%); **mp**: 180 ºC (decomp); **IR** (KBr): 2949-3303 (br), 2234, 1751, 1593, 1498, 1264, 1239, 1094, 1004, 833 cm^{-1}; **^{1}H NMR** ($CDCl_3$+TFA) δ: 8.33 (d, *J* = 12.0 Hz, 1H), 8.17-8.22 (2"+6"-H), 8.10 (br, 1H, COOH), 7.92 (dd, *J* = 16.0, 12.0 Hz, 1H), 7.61-7.68 (m, 3H); **^{13}C NMR** ($CDCl_3$+TFA) δ: 167.0, 161.8, 157.2, 138.4, 134.9, 132.4, 130.9, 123.3, 122.0, 108.0, 106.4; **Anal. Calcd** for $C_{13}H_8N_5O_2Cl$: C, 51.76; H, 2.67; N, 23.21. Found: C, 51.94; H, 2.95; N, 22.95.

Ethyl (2*E/Z*,4*E*)-5-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]-2-nitropenta-2,4-dienoate (8)

To anhydrous tetrahydrofuran (50 mL) under an argon atmosphere was added dropwise titanium(IV) chloride (1.62 g, 935 μL, 8.53 mmol) in carbon tetrachloride (10 mL) at 0 ºC. To the resulting yellow suspension was added **3a** (1.00 g, 4.26 mmol) and ethyl nitroacetate (0.66 g, 550 μL, 4.96 mmol), and finally *N*-methylmorpholine (1.94 g, 2.1 mL, 19.2 mmol) in tetrahydrofuran (20 mL) in 1 h. The mixture was stirred for additional 1 h, and allowed to warm up to rt, and stirred overnight. Water (50 mL) and ether (50 mL) was added, the two layers were separated, the aqueous layer was extracted 2 times with ether, and the collected organic layer was washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was recrystallised from 2-propanol to yield pale yellow crystals as a mixture of the two isomers in a ratio of 1 : 0.7 (1.055 g, 78 %); **mp**: 78-80 ºC; **IR** (KBr): 1720, 1623, 1535, 1496, 1372, 1280, 1224, 1153, 1097, 998 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: *trans-trans* isomer: 8.09-8.13 (2"+6"-H), 7.94 (dd. *J* = 11.7, 15.0 Hz, 1H), 7.54-7.58 (3"+5"-H), 7.43 (d, *J* = 11.7 Hz, 1H), 7.30 (d, *J* = 15.0 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H); *cis-trans* isomer: 8.09-8.13 (2"+6"-H), 7.75 (d, *J* = 9.5 Hz, 1H), 7.50-7.58 (m, 3H), 7.34 (dd, *J* = 9.5, 15.4 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H); **^{13}C**

NMR ($CDCl_3$) δ: 163.0, 162.7, 159.1, 137.2, 135.2, 133.2, 131.3, 130.4, 127.0, 121.5, 63.5, 14.3; **Anal. Calcd** for $C_{14}H_{12}N_5O_4Cl$: C, 48.08; H, 3.46; N, 20.03. Found: C, 48.10; H, 3.46; N, 19.85.

Synthesis of (2E/Z,4E)-5-[2-(4-chlorophenyl)-2H-tetrazol-5-yl]penta-2,4-dienenitrile (**9, 10**)

Method A: To tetrahydrofuran (15 mL) was added lithium diisopropylamide (2M solution in heptane-tetrahydrofuran-ethylbenzene, 2.55 mL, 5.1 mmol) at –78 ºC under an argon atmosphere and a solution of trimethylsilylacetonitrile (0.567 g, 683 μL, 5.00 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at –78 ºC for 40 min. Then the suspension of **3a** (1.17 g, 4.99 mmol) in tetrahydrofuran (10 mL) was added to the reaction mixture. Increase of the reaction temperature could be observed. This mixture was stirred for additional 1 h at –78 ºC, and then it was allowed to warm up to rt, and stirred overnight. The reaction mixture was quenched with aqueous ammonium chloride solution (20 mL, 10%) and extracted 6 times with dichloromethane (20 mL). The collected organic layer was washed with brine (50 mL), dried over sodium sulfate and the solvent was evaporated. The two isomers were separated with flash column chromatography on Kieselgel 60H with a mixture of dichloromethane and hexane (1:1) as the eluent.

Method B: A mixture of **13a** (0.40 g, 1.45 mmol), triethylamine (0.47 g, 650 μL, 4.64 mmol) and dichloromethane (10 mL) was cooled to 0 ºC under an argon atmosphere and trifluoroacetic anhydride (0.365 g, 242 μL, 1.74 mmol) was added dropwise with stirring. The temperature of the reaction mixture increased spontaneously and the solution became clear brown. Stirring was continued for additional 1 h at 0 ºC, and the reaction was monitored by TLC. The mixture was poured onto ice water and extracted with dichloromethane (3 x 10 mL), the collected organic layer was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was treated with ether, and the precipitated solid was filtered off.

(2*E*,4*E*)-5-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienenitrile (9a)

This compound was synthesized by both Method A and Method B. Method A yielded 0.086 g of product (21%), whereas a higher yield (0.297 g, 79%) was obtained by Method B. Colorless crystals; **mp**: 166-168 ºC (from acetonitrile); **IR** (KBr): 2216, 1603, 1498, 998, 827 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.07-8.11 (2"+6"-H), 7.53-7.57 (3"+5"-H), 7.47 (dd, *J* = 12.0, 16.0 Hz, 1H), 7. 22 (dd, *J* = 12.0, 16.0 Hz, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 5.69 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$) δ: 163.1, 148.5, 136.3, 135.3, 133.5, 130.3, 124.8, 121.4, 117.7, 103.4; **Anal. Calcd** for $C_{12}H_8N_5Cl$: C, 55.93; H, 3.13; N, 27.18. Found: C, 55.76; H, 2.86; N, 26.80.

(2*Z*,4*E*)-5-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienenitrile (10a)

Method A: 0.096 g (22%, colorless crystals); **mp**: 148-149 ºC (from acetonitrile); **IR** (KBr): 3067, 2210, 1582, 1497, 1420, 1091, 998, 955, 830 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.10-8.15 (2"+6"-H), 7.86 (dd, *J* = 11.4, 16.0 Hz, 1H), 7.54-7.58 (3"+5"-H), 7.01-7.12 (m, 2H), 5.52 (d, *J* = 10.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$) δ: 166.1, 150.4, 139.2, 138.1, 134.7, 133.2, 128.3, 124.3, 118.9, 104.6; **Anal. Calcd** for $C_{12}H_8N_5Cl$: C, 55.93; H, 3.13; N, 27.18. Found: C, 55.83; H, 2.95; N, 27.27.

(2*E*,4*E*)-5-[2-(4-Isopropylphenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienenitrile (9b)

This compound was prepared by Method B starting from **13b** (0.300 g, 1.06 mmol). The residue obtained from evaporation of the reaction mixture was treated with petroleum ether to give yellow crystals (0.247 g, 88 %); **mp**: 152-153 ºC (from acetonitrile); **IR** (KBr): 2973, 2216, 1603, 1516, 1435, 1062, 1002, 839, 809 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.01-8.05 (2"+6"-H), 7.48 (dd, *J* = 11.2, 15.2 Hz, 1H), 7.39-7.44 (3"+5"-H), 7.21 (dd, *J* = 11.2, 15.6 Hz, 1H), 7.03 (d, *J* = 15.2 Hz, 1H), 5.67 (d, *J* = 15.6 Hz, 1H), 3.10 (m, 1H, CH), 1.30 (d, *J* = 7. 0 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 162.8, 151.6, 148.7, 134.8, 133.0, 128.0, 125.2, 120.2, 117.7, 103.0; **Anal. Calcd** for $C_{15}H_{15}N_5$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.70; H, 5.67; N, 26.12.

Ethyl (2*E*,4*E*)-5-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienoate (11a)

The mixture of **3a** (1.15 g, 4.90 mmol), (carbethoxymethylene)triphenylphosphorane (2.10 g, 6.03 mmol) and dichloromethane (70 mL) was stirred for 2 h. The reaction was followed by TLC. The formation of the 2*Z*,4*E* isomer could be observed only in traces. The product was purified by flash column chromatography on Kieselgel 60H with dichloromethane as the eluent. The title compound was separated as pale yellow crystals (1.409 g, 95%), **mp**: 102-103 ºC (from acetonitrile); **IR** (KBr): 2990, 1718, 1629, 1497, 1366, 1322, 1238, 1215, 1174, 1137, 1008, 998, 827 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.07-8.11 (2"+6"-H), 7.50-7.61 (m, 3H), 7.45 (dd, *J* = 11.2, 14.3 Hz, 1H), 7.01 (d, *J* = 14.7 Hz, 1H), 6.19 (d, *J* = 14.3 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$) δ: 166.6, 163.7, 142.5, 136.1, 135.4, 134.6, 130.3, 126.0, 123.7, 121.3, 61.1, 14.6; **Anal. Calcd** for $C_{14}H_{13}N_4OCl$: C, 55.18; H, 4.30; N, 18.39. Found: C, 55.47; H, 4.12; N, 18.41.

Ethyl (2*E*,4*E*)-5-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienoate (11b)

To the solution of **3b** (0.40 g, 1.65 mmol) and lithium bromide (0.143 g, 1.73 mmol) in acetonitrile (15 mL) at 50 ºC was added (carbethoxymethylene)triphenylphosphorane (0.603 g, 1.73 mmol). The mixture was stirred at this temperature for 2 h. The reaction was monitored by TLC. The formation of the two isomers could be observed. The title compound was separated by flash column chromatography on Kieselgel 60H by using dichloromethane as the eluent. The product was obtained as colorless crystals (0.348 g, 67%); **mp**: 77-78 ºC (from hexane); **IR** (KBr): 2961, 1705, 1621, 1516, 1362, 1323, 1308, 1236, 1215, 1170, 1131,

1029, 1005, 836 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.01-8.05 (2"+6"-H), 7.38-7.55 (m, 4H), 7.02 (d, *J* = 14.6 Hz, 1H), 6.17 (d, *J* = 14.0 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 2H, CH_2), 3.00 (m, 1H, CH), 1.30 (m, 9H); **^{13}C NMR** ($CDCl_3$) δ: 166.7, 163.4, 151.3, 142.7, 134.9, 134.1, 127.9, 125.6, 124.1, 120.1, 60.9, 34.2, 24.1, 14.6; **Anal. Calcd** for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.58; H, 6.52; N, 17.86.

(2*E*,4*E*)-5-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienoic acid (12a)

To a solution of **11a** (0.40 g, 1.31 mmol) in ethanol (25 mL), aqueous sodium hydroxide solution (1 mL, 5.0 mmol, 20%) was added, and the mixture was stirred overnight and evaporated *in vacuo*. The residue was treated with water and was adjusted to pH=3 with concentrated HCl. The precipitated product was filtered off and washed with water until neutral pH to give colorless crystals (0.36 g, 100%), **mp**: 196-197 ºC (from acetic acide); **IR** (KBr): 2567-3132 (br), 1682, 1619, 1495, 1420, 1316, 1258, 1225, 1097, 998, 830 cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ: 8.11-8.16 (2"+6"-H), 7.74-7.78 (3"+5"-H), 7.39-7.65 (m, 2H), 7.28 (d, *J* = 16.0 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** (DMSO-d_6) δ: 168.6, 164.2, 142.1, 135.8, 135.7, 135.5, 131.1, 129.1, 123.4, 122.5;

(2*E*,4*E*)-5-[2-(4-Isopropylphenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienoic acid (12b)

This compound was prepared according the procedure described for **12a** starting from **11b** (0.45 g, 1.44 mmol) to give colorless crystals (0.397 g, 97%); **mp**: 144-146 ºC; **IR** (KBr): 2559-2961 (br), 1690, 1621, 1516, 1426, 1308, 1278, 1008, 998, 833 cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ: 8.00-8.05 (2"+6"-H), 7.43-7.60 (m, 4H), 7.31 (d, *J* = 15.0 Hz, 1H), 6.33 (d, *J* = 14.4 Hz, 1H), 3.03 (m, 1H, CH), 1.27 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (DMSO-d_6) δ: 168.2, 163.9, 151.8, 143.1, 135.2, 135.0, 128.9, 127.6, 124.2, 120.8, 34.1, 24.6; **Anal. Calcd** for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 62.95; H, 5.61; N, 19.69.

(2*E*,4*E*)-5-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienamide (13a)

A mixture of **12a** (0.569 g, 2.06 mmol), thionyl chloride (0.318 g, 195 μL, 2.67 mmol), and toluene (15 mL) was refluxed for 2 h. The resulting brown solution was cooled down in an ice bath, and ammonia gas was bubbled through the solution for 10 min. A yellow precipitate was formed. The mixture was evaporated *in vacuo* to dryness, water was added to the residue and the product was filtered off to give pale yellow crystals (0.526 g, 93%); **mp**: 140-142 ºC (from ethanol); **IR** (KBr): 3393, 3159, 1669, 1609, 1495, 1374, 1227, 1089, 995, 827 cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ: 8.13-8.18 (2"+6"-H), 7.75-7.80 (3"+5"-H), 7.68 (br, 1H, NH_2), 7.54 (dd, *J* = 12.0, 16.0 Hz, 1H), 7.35 (dd, *J* = 12.0, 16.0 Hz, 1H), 7.22 (d, *J* = 16.0 Hz, 1H), 7.21 (br, 1H, NH_2), 6.41 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** (DMSO-d_6) δ: 167.2, 164.3, 138.6, 136.0, 135.8, 135.5, 131.1, 130.9, 122.6, 122.5.

(2*E*,4*E*)-5-[2-(4-Isopropylphenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienamide (13b)

This compound was prepared according the procedure described for **13a** starting from **12b** (0.500 g, 1.76 mmol). The product was isolated by extraction of the evaporated reaction mixture with ethyl acetate and the organic layer was dried over sodium sulfate and evaporated to dryness. The residue was treated with ether and the product was filtered off to give yellow crystals (0.383 g, 77%); **mp**: 128-130 ºC (from 2-propanol); **IR** (KBr): 3393, 3183, 2955, 1660, 1606, 1513, 1392, 1224, 995, 839 cm^{-1}; **^{1}H NMR** ($DMSO-d_6$) δ: 8.00-8.05 (2"+6"-H), 7.69 (br, 1H, NH_2), 7.47-7.60 (m, 3H), 7.36 (dd, *J* = 11.0, 14.6 Hz, 1H), 7.25 (br, 1H, NH_2), 7.20 (d, *J* = 15.0 Hz, 1H), 6.41 (d, *J* = 14.6 Hz, 1H), 3.03 (m, 1H, CH), 1.27 (d, *J* = 6.8 Hz, 6H, CH_3); **^{13}C NMR** ($DMSO-d_6$) δ: 167.2, 164.0, 151.7, 138.7, 135.6, 135.0, 130.7, 128.8, 122.7, 120.8, 34.1, 24.5; **Anal. Calcd** for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.20; H, 6.00; N, 24.65.

Ethyl (2*Z*,4*E*)-2-acetyl-5-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienoate (14a)

A solution of titanium(IV) chloride (1.62 g, 935 μL, 8.53 mmol) in carbon tetrachloride (10 mL) was added dropwise at 0 ºC to anhydrous tetrahydrofuran (50 mL) under an argon atmosphere to yield a yellow suspension. To this mixture, **3a** (1.00 g, 4.26 mmol), ethyl acetoacetate (0.61 g, 600 μL, 4.69 mmol) and then a solution of pyridine (1.35 g, 1.38 mL, 17.05 mmol) in tetrahydrofuran (10 mL) was added in a period of 1 h. The mixture was stirred for additional 1 h, allowed to warm up to rt, and stirred overnight. Water (50 mL) and ether (50 mL) was added, and the two layers was separated. The aqueous layer was extracted with ether (2 x 20 mL), and the collected organic layer was washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was recrystallized from 2-propanol to yield beige crystals (1.30 g, 88%), **mp**: 80-82 ºC; **IR** (KBr): 2985, 1711, 1684, 1570, 1495, 1269, 1227, 1095, 1005, 824 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.08-8.12 (2"+6"-H), 7.88 (dd, *J* = 11.7, 15.7 Hz, 1H), 7.53-7.57 (3"+5"-H), 7.41 (d, *J* = 11.7 Hz, 1H), 7.19 (d, *J* = 15.7 Hz,1H), 4.44 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$) δ: 195.5, 163.4, 141.5, 136.4, 136.3, 135.3, 131.6, 130.3, 128.0, 121.4, 62.1, 28.4, 14.6; **Anal. Calcd** for $C_{16}H_{15}N_4O_3Cl$: C, 55.42; H, 4.36; N, 16.16. Found: C, 55.23; H, 4.24; N, 16.01.

Ethyl (2*E*,4*E*)-2-acetyl-5-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]penta-2,4-dienoate (14b)

This compound was prepared according the procedure described for **14a** starting from **3b** (0.60 g, 2.48 mmol) to give a yellow oil, which was purified by flash coloumn chromatography on Kieselgel 60H with dichloromethane as the eluent. The purified product was treated with hexane and ether upon which colorless crystals were obtained (0.786 g, 89%); **mp**: 88-89 ºC (from hexane); **IR** (KBr): 2967, 1720, 1690, 1600, 1513, 1359, 1272, 1230, 1215, 1146, 1059, 995, 839 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.02-8.07 (2"+6"-H), 7.74 (dd, *J* = 12.0, 15.4 Hz, 1H), 7.44 (d, *J* = 12.0 Hz, 1H), 7.38-7.42 (3"+5"-H), 7.16 (d, *J* = 15.4 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 2H, CH_2), 3.00 (m, 1H, CH), 2.49 (s, 3H, $COCH_3$), 1.37 (t, *J* = 7.0 Hz, 3H, CH_3), 1.30 (d, *J* = 7.0 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 200.3, 164.9, 163.1, 151.5, 141.9, 136.5, 134.9, 130.8,

128.2, 128.0, 120.2, 61.9, 34.3, 31.5, 24.1, 14.5; **Anal. Calcd** for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.59; H, 6.25; N, 15.92.

(3*E*,5*E*)-6-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]hexa-3,5-dien-2-one (15a)

A mixture of **14a** (0.50 g, 1.44 mmol), aqueous HCl (30 mL, 18%) in ethanol (20 mL) was refluxed for 20 h. The reaction was monitored by TLC. The mixture was poured onto ice water, extracted with ethyl acetate (5 x 30 mL). The collected organic layer was washed with aqueous sodium hydrogencarbonate solution (20 mL, 10%) and water, and dried over sodium sulfate. The solvent was removed *in vacuo* to give colorless crystals (0.23 g, 58%), **mp**: 105-107 ºC (from acetonitrile); **IR** (KBr): 1675, 1492, 1417, 1362, 1254, 1089, 998, 827 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.08-8.11 (2"+6"-H), 7.55 (dd, *J* = 11.5, 15.2 Hz, 1H), 7.54-7.56 (3"+5"-H), 7.30 (dd, *J* = 11.5, 15.8 Hz, 1H), 7.05 (d, *J* = 15.8 Hz, 1H), 6.42 (d, *J* = 15.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$) δ: 198.4, 163.7, 141.1, 136.1, 135.4, 135.0, 134.1, 130.3, 124.4, 121.3, 28.2; **Anal. Calcd** for $C_{13}H_{11}N_4OCl$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.41; H, 3.95; N, 20.08.

(3*E*,5*E*)-6-[2-(4-Isopropylphenyl)-2*H*-tetrazol-5-yl]hexa-3,5-dien-2-one (15b)

A mixture of **14b** (0.786 g, 2.22 mmol), aqueous HCl (15 mL, 18%) in ethanol (20 mL) was refluxed for 40 h. The reaction was monitored by TLC. The mixture was poured onto ice water and extracted with dichloromethane (2 x 20 mL). The collected organic layer was washed with aqueous sodium hydrogencarbonat solution (20 mL, 10%) and water, and dried over Na_2SO_4. The solvent was removed *in vacuo* to dryness. The residue (a mixture of oil and crystalls) was purified two times by flash column chromatography on silica gel with a mixture of hexane and ethyl acetate (5:1) to yield yellow crystals (0.24 g, 39%); **IR** (KBr): 2961, 1678, 1670, 1603, 1510, 1248, 1059, 998, 836 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.01-8.07 (2"+6"-H), 7.62 (dd, *J* = 9.6, 14.4 Hz, 1H), 7.39-7.43 (3"+5"-H), 7.10 (dd, *J* = 9.6, 15.4 Hz, 1H), 6.75 (d, *J* = 14.4 Hz, 1H), 6.42 (d, *J* = 15.4 Hz, 1H), 3.08 (m, 1H, CH), 2.36 (s, 3H, CH_3), 1.30 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** ($CDCl_3$) δ: 198.4, 163.4, 141.7, 141.3, 134.9, 134.5, 133.9, 128.0, 124.9, 120.2, 34.3, 28.1, 24.1. As all our efforts for purification of this product for analytical purposes failed, the crude product was used for further transformations.

2-(4-Chlorophenyl)-5-{(1*E*,3*Z*)-3-[methyl(oxido)imino]prop-1-en-1-yl}-2*H*-tetrazole (16a)

A mixture of **3a** (0.30g, 1.28 mmol), *N*-methylhydroxylamine hydrochloride (0.128 g, 1.54 mmol) and sodium acetate (0.188 g, 2.30 mmol) in ethanol (30 mL) was allowed to stand at rt overnight. The solution was removed *in vacuo*, and water and dichloromethane were added to the residue. The two layers were separated. The organic layer was extracted with dichloromethane (2 x 20 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was treated with hexane and the colorless crystalline product was

filtered off to give 0.243 g (72%); **mp**: 86-87 ºC (from acetonitrile); **IR** (KBr): 1561, 1498, 1402, 1377, 1239, 1152, 1092, 995, 980, 947, 833 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.06-8.10 (2'+6'-H), 7.93 (dd, *J* = 9.5, 16.1 Hz, 1H), 7.51-7.55 (3'+5'-H), 7.39 (d, *J* = 9.5 Hz, 1H), 7.27 (d, *J* = 16.1 Hz, 1H), 3.85 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 164.1, 135.9, 135.5, 135.3, 130.2, 125.8, 121.2, 120.9, 53.5; **Anal. Calcd** for $C_{11}H_{10}N_5OCl$: C, 50.10; H, 3.82; N, 26.56. Found: C, 50.14; H, 3.61; N, 26.26.

5-{(1*E*,3*Z*)-3-[Benzyl(oxido)imino]prop-1-en-1-yl}-2-(4-chlorophenyl)-2*H*-tetrazole (16b)

A mixture of **3a** (1.50 g, 6.39 mmol), *N*-benzylhydroxylamine (1.02 g, 8.31 mmol), Na_2SO_4 (3.75 g) and dichloromethane (30 mL) was allowed to stand at rt for 25 min. The sodium sulfate was filtered off and washed several times with dichloromethane. The solvent was evaporated and the residue was recrystallized from acetonitrile to give pale yellow crystals (1.88 g, 87 %); **mp**: 154 ºC; **IR** (KBr): 1615, 1534, 1492, 1459, 1417, 1242, 1185, 1128, 1086, 998, 833, 695 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.05-8.09 (2'+6'-H), 7.92 (dd, *J* = 9.2, 16.5 Hz, 1H), 7.40-7.54 (m, 7H), 7.35 (d, *J* = 9.2 Hz, 1H), 7.26 (d, *J* = 16.5 Hz, 1H), 5.02 (s, 2H, CH_2); **^{13}C NMR** ($CDCl_3$) δ: 164.2, 136.0, 135.4, 134.5, 133.0, 130.2, 129.6, 129.5, 129.4 (2C), 125.9, 121.3, 70.6; **Anal. Calcd** for $C_{17}H_{14}N_5OCl$: C, 60.09; H, 4.15; N, 20.61. Found: C, 59.85; H, 3.92; N, 20.70.

2-(4-Isopropylphenyl)-5-{(1*E*,3*Z*)-3-[methyl(oxido)imino]prop-1-en-1-yl}-2*H*-tetrazole (16c)

This compound was prepared according the procedure described for **16a** starting from **3b** (0.50 g, 2.06 mmol), after evaporation of the organic extract to dryness the residue was treated with ether, and the solid product was filtered off to yield colorless crystals (0.46 g, 82%); **mp**: 131-132 ºC (from acetonitrile); **IR** (KBr): 2955, 1561, 1513, 1471, 1429, 1411, 1182, 1143, 1062, 1005, 980, 956, 833 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.01-8.06 (2'+6'-H), 7.94 (dd, *J* = 9.2, 16.4 Hz, 1H), 7.36-7.42 (m, 3H), 7.26 (d, *J* = 16.4 Hz, 1H), 3.84 (s, 3H), 3.00 (m, 1H, CH), 1.29 (d, *J* = 7. 0 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 163.8, 151.3, 135.7, 134.9, 127.9, 125.5, 121.4, 120.1, 53.4, 34.2, 24.1; **Anal. Calcd** for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81. Found: C, 61.77; H, 6.41; N, 25.71.

5-{(1*E*,3*Z*)-3-[Benzyl(oxido)imino]prop-1-en-1-yl}-2-(4-isopropylphenyl)-2*H*-tetrazole (16d)

This compound was prepared according the procedure described for **16b** starting from **3b** (0.60 g, 2.48 mmol) to give colorless crystals (0.561 g, 65%); **mp**: 136-138 ºC (from acetonitrile); **IR** (KBr): 2961, 1513, 1471, 1423, 1326, 1203, 1131, 998, 980, 833, 701 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.99-8.04 (2'+6'-H), 7.94 (dd, *J* = 9.6, 16.2 Hz, 1H), 7.33-7.48 (m, 8H), 7.26 (d, *J* = 16.2 Hz, 1H), 5.02 (s, 2H, CH_2), 2.99 (m, 1H, CH), 1.28 (d, *J* = 7. 0 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 163.8, 151.2, 134.9, 134.6, 133.0, 129.5, 129.4, 129.3, 127.9, 125.4, 121.7, 120.0, 70.4, 34.2, 24.1; **Anal. Calcd** for $C_{20}H_{21}N_5O$: C, 69.14; H, 6.09; N, 20.16. Found: C, 68.92; H, 6.19; N, 20.21.

(5R,8S)-5-Acetyl-8-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]-2-phenyl-5,8-dihydro-1*H*-[1,2,4]triazolo [1,2-*a*]pyridazine-1,3(2*H*)-dione (17a)

A mixture of **15a** (0.100 g, 0.36 mmol), 4-phenyl-1,2,4-triazoline-3,5-dione (0.064 g, 0.37 mmol), and dichloromethane (8 mL) was stirred for 1 day at rt. The reaction was monitored by TLC. The starting red solution continously turned to pale yellow. The reaction mixture was evaporated to dryness to give a yellow oil, which was treated with ether to give a solid. The product was filtered off, and washed several times with ether. Recrystallisation from 2-propanol gave colorless crystals (0.125 g, 76%); **mp**: 157-159 ºC; **IR** (KBr): 1786, 1722, 1495, 1428, 1004 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.03-8.07 (2"+6"-H), 7.39-7.55 (m, 7H), 6.32 (ddd, *J* = 2.5, 4.8, 7.3 Hz, 1H), 6.04-6.13 (m, 2H), 4.97 (dd, *J* = 3.0, 5.5 Hz, 1H), 2.35 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 200.4, 168.0, 162.8, 136.1, 134.9, 130.7, 130.0, 129.2, 128.5, 125.4, 124.6, 121.8, 121.1, 64.7, 49.4, 25.6; **Anal. Calcd** for $C_{21}H_{16}N_7O_3Cl$: C, 56.07; H, 3.58; N, 21.80. Found: C, 56.09; H, 3.47; N, 21.54.

Ethyl (5R,8S)-8-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1*H*-[1,2,4]-triazolo [1,2-*a*]pyridazine-5-carboxylate (17b)

This compound was synthesized by using the procedure described for **17a** starting from **11a** (0.200 g, 0.66 mmol), and using a reaction time of 3 days. The product was recrystallized from acetonitrile to give colorless crystals (0.195 g, 62%); **mp**: 160-161 ºC; **IR** (KBr): 2922, 1787, 1719, 1503, 1424, 1283, 1219, 1158, 1093, 1000, 836 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.04-8.08 (2"+6"-H), 7.35-7.53 (m, 7H), 6.32 (ddd, *J* = 2.4, 4.8, 10.2 Hz, 1H), 6.10 (ddd, *J* = 2.4, 4.6, 10.2, 1H), 5.91 (dd, *J* = 2.4, 4.8 Hz, 1H), 5.21 (dd, *J* = 2.4, 4.6 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$) δ: 165.9, 162.9, 152.2, 135.9, 135.0, 130.8, 129.8, 129.1, 128.3, 125.5, 124.8, 121.3, 121.2, 62.7, 55.8, 50.9, 14.0; **Anal. Calcd** for $C_{22}H_{18}N_7O_4Cl$: C, 55.06; H, 3.78; N, 20.43. Found: C, 54.79; H, 3.78; N, 20.19.

(5R,8S)-5-Acetyl-8-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]-2-phenyl-5,8-dihydro-1*H*-[1,2,4]triazolo[1,2-*a*]-pyridazine-1,3(2*H*)-dione (17c)

This compound was synthesized by using the procedure described for **17a** starting from **15b** (0.135 g, 0.48 mmol). The product was recrystallised from acetonitrile to give colorless crystals (0.132 g, 60%); **mp**: 160-162 ºC; **IR** (KBr): 2931, 1783, 711, 1504, 1423, 1290, 1143, 1008, 875, 836, 764 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.97-8.01 (2"+6"-H), 7.37-7.58 (m, 7H), 6.39 (ddd, *J* = 2.6, 4.6, 5.6 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (dd, *J* = 2.6, 5.4 Hz, 1H), 2.99 (m, 1H, CH), 2.34 (s, 3H, CH_3), 1.28 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** ($CDCl_3$) δ: 201.1, 162.8, 153.2, 151.8, 134.8, 131.2, 129.5, 128.7, 128.0, 125.7, 125.7, 122.1, 120.3, 65.2, 49.7, 34.3, 25.8, 24.1; **Anal. Calcd** for $C_{24}H_{23}N_7O_3$: C, 63.01; H, 5.07; N, 21.43. Found: C, 63.11; H, 5.18; N, 21.77.

Ethyl (5R,8S)-8-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-5-carboxylate (17d)

This compound was synthesized by using the procedure described for **17a** starting from **11b** (0.15 g, 0.48 mmol) by using a reaction time of 5 days to give colorless crystals (0.181 g, 77%); **mp**: 114 ºC (from hexane); **IR** (KBr): 2955, 1783, 1720, 1504, 1495, 1417, 1269, 1212, 1140, 1104, 1011, 854, 827 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.98-8.02 (2"+6"-H), 7.34-7.55 (m, 7H), 6.32 (ddd, *J* = 2.6, 4.7, 9.9 Hz, 1H), 6.10 (dd, *J* = 2.2, 9.9 Hz, 1H), 5.92 (d, *J* = 2.2 Hz, 1H), 5.20 (m, 1H), 4.31 (q, *J* = 6.8 Hz, 2H), 2.98 (m, 1H, CH), 1.29 (m, 9H); **^{13}C NMR** ($CDCl_3$) δ: 168.0, 166.3, 162.8, 152.5, 151.5, 135.0, 131.3, 129.4, 128.6, 127.9, 125.8, 125.4, 121.5, 120.4, 63.0, 56.2, 51.3, 34.2, 24.1, 14.4; **Anal. Calcd** for $C_{25}H_{25}N_7O_4$: C, 61.59; H, 5.17; N, 20.11. Found: C, 61.73; H, 5.20; N, 19.79.

Ethyl (3aS,4S,7R,7aS)-7-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-carboxylate (18a)

A mixture of **11a** (0.100 g, 0.33 mmol) and *N*-methylmaleimide (0.040 g, 0.36 mmol) was stirred in 1-n-butyl-3-methylimidazolinium hexafluorophosphate (BMIM*PF_6, 1 mL) at 120 ºC for 9.5 h. The product was extracted with ether (6 x15 mL), the residue obtained after evaporation was treated with hot acetonitrile. Upon cooling a precipitate was formed which was filtered off to give pale yellow crystals (0.039 g, 29%); **mp**: 133-135 ºC (from acetonitrile); **IR** (KBr): 1780, 1735, 1705, 1507, 1438, 1383, 1323, 1290, 1197, 1092, 1005, 983, 833 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.09-8.13 (2"+6"-H), 7.51-7.56 (3"+5"-H), 6.75 (dd, *J* = 2.9, 9.5 Hz, 1H), 6.64 (dd, *J* = 2.6, 9.5 Hz, 1H), 4.35 (m, 2H), 4.00 (m, 1H), 3.90 (dd, *J* = 2.4, 4.7 Hz 2H), 3.30 (m, 1H), 2.85 (s, 3H, N-CH_3), 1.39 (t, *J* = 7.2 Hz, 3H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 176.0, 175.2, 169.8, 164.9, 135.5, 135.3, 129.8, 128.3, 127.5, 121.1, 121.0, 61.6, 43.7, 42.4, 40.9, 34.0, 24.9, 14.1; **Anal. Calcd** for $C_{19}H_{18}N_5O_4Cl$: C, 54.88; H, 4.36; N, 16.84. Found: C, 54.53; H, 4.30; N, 16.61.

Ethyl (3aS,4S,7R,7aS)-7-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-carboxylate (18b)

A mixture of **11b** (0.15 g, 0.48 mmol) and *N*-methylmaleimide (0.059 g, 0.53 mmol) was stirred in BMIM*PF_6 (1 mL) at 110 ºC for 21 h. The reaction mixture was extracted with ether 6 times. The ether was removed *in vacuo*. The residue was purified by flash vacuum chromatography on Kieselgel 60H with a mixture of hexane and ethyl acetate (2:1) as the eluent. After evaporation to dryness the product was isolated as colorless crystals (0.038 g, 19%); **mp**: 188-190 ºC; **IR** (KBr): 2955, 1774, 1726, 1702, 1516, 1432, 1383, 1320, 1287, 1188, 1095, 1005, 977, 830, 719 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.03-8.07 (2"+6"-H), 7.37-7.42 (3"+5"-H), 6.76 (dd, *J* = 3.0, 9.6 Hz, 1H), 6.63 (dd, *J* = 3.0, 9.6 Hz, 1H), 4.37 (m, 2H), 3.98 (m, 1H), 3.90 (m, 2H), 3.31 (m, 1H), 3.00 (m, 1H, CH), 2.84 (s, 3H, N-CH_3), 1.39 (t, *J* = 7.4 Hz, 3H), 1.29 (d, *J*

= 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$) δ: 176.4, 175.5, 170.3, 164.9, 151.1, 135.2, 128.5, 128.1, 127.8, 120.3, 61.9, 44.1, 42.8, 41.2, 34.3, 24.2, 25.2, 24.1, 14.5; **Anal. Calcd** for $C_{22}H_{25}N_5O_4$: C, 62.40; H, 5.95; N, 16.54. Found: C, 62.55; H, 5.91; N, 16.56.

*General procedure for the 1,3-dipolar cycloaddition of nitrones (**16a-d**) with N-methylmaleimide*

The solution of the appropriate nitrone (**16a-d**, 1 mmol) and *N*-methylmaleimide (0.12 g, 1.1 mmol) in toluene (20 mL) was refluxed and the reaction was followed by TLC. The mixture was evaporated to dryness. The residue contained two isomers, which were separated by flash chromatography on Kieselgel 60H with a mixture of hexane and ethyl acetate (2:1) as the eluent.

(3*S*,3a*S*,6a*R*)-3-{(*E*)-2-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]vinyl}-2,5-dimethyldihydro-2*H*-pyrrolo-[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (20a)

Starting compound: **16a** (0.26 g), reaction time: 27.5 h, colorless crystals (0.15 g, 39%); **mp**: 183 ºC (from acetonitrile); **IR** (KBr):1783, 1705, 1495, 1438, 1383, 1287, 1212, 1092, 998, 833 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.10 (2”’+6”’-H), 7.54 (3”’+5”’-H), 7.06 (dd, *J* = 9.0, 16.0 Hz, 1H, 1’-H), 6.90 (d, *J* = 16.0 Hz, 1H, 2’-H), 4.88 (d, *J* = 7.0 Hz, 1H, 6a-H), 4.00 (br, 1H, 3-H), 3.58 (d, *J* = 7.0 Hz, 1H, 3a-H), 3.07 (s, 3H, CH_3), 2.70 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 175.0, 163.0, 136.0, 135.3, 133.4, 130.2, 121.2, 121.0, 75.9, 70.5, 55.3, 39.8, 25.4; **Anal. Calcd** for $C_{16}H_{15}N_6O_3Cl$: C, 51.28; H, 4.03; N, 22.42. Found: C, 51.16; H, 4.06; N, 22.10.

(3*R*,3a*S*,6a*R*)-3-{(*E*)-2-[2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl]vinyl}-2,5-dimethyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (21a)

Starting compound: **16a** (0.26 g), reaction time 27.5 h, colorless crystals (0.15 g, 39%); **mp**: 175-177 ºC (from acetonitrile); **IR** (KBr): 1780, 1702, 1498, 1438, 1287, 1227, 1095, 1038, 998, 833 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.08 (2”’+6”’-H), 7.55 (3”’+5”’-H), 6.88 (d, *J* = 16.0 Hz, 1H, 2’-H), 6.78 (dd, *J* = 8.4, 16.0 Hz, 1H, 1’-H), 4.86 (d, *J* = 7.0 Hz, 1H, 6a-H), 3.71 (dd, *J* = 7.0, 8.0 Hz, 1H, 3a-H), 3.46 (dd, *J* = 8.0, 8.4 Hz, 1H, 3-H), 3.08 (s, 3H, CH_3), 2.73 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 175.2, 173.2, 163.1, 136.0, 135.4, 131.8, 130.2, 121.7, 121.4, 76.2, 73.4, 53.5, 42.7, 25.4; **Anal. Calcd** for $C_{16}H_{15}N_6O_3Cl$: C, 51.28; H, 4.03; N, 22.42. Found: C, 51.02; H, 3.85; N, 22.70.

(3*S*,3a*S*,6a*R*)-3-{(*E*)-2-[2-(4-Isopropylphenyl)-2*H*-tetrazol-5-yl]vinyl}-2,5-dimethyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (20b)

Starting compound: **16c** (0.27 g), reaction time: 8 h, colorless crystals (0.15 g, 38%); **mp**: 90-91 ºC (from acetonitrile); **IR** (KBr): 2967, 1783, 1708, 1513, 1438, 1380, 1290, 1131, 1023, 1005, 971, 833 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.00-8.05 (2”’+6”’-H), 7.39-7.43 (3”’+5”’-H), 7.05 (dd, *J* = 8.4, 16.0 Hz, 1H, 2’-H), 6.89

(d, *J* = 16.0 Hz, 1H, 1'-H), 4.88 (d, *J* = 7.4 Hz, 1H, 6a-H), 4.10 (m, 1H, 3-H), 3.58 (d, *J* = 7.4 Hz, 1H, 3a-H), 3.07 (s, 3H, N-CH_3), 3.00 (m, 1H, CH), 2.70 (s, 3H, N-CH_3), 1.30 (d, *J* = 6.8 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 175.2, 162.8, 151.4, 134.9, 132.9, 128.0, 121.5, 120.1, 76.0, 60.7, 55.3, 34.2, 25.5, 24.1 (2C); **Anal. Calcd** for $C_{19}H_{22}N_6O_3$: C, 59.67; H, 5.80; N, 21.98. Found: C, 59.62; H, 5.80; N, 21.73.

(3*R*,3a*S*,6a*R*)-3-{(*E*)-2-[2-(4-Isopropylphenyl)-2*H*-tetrazol-5-yl]vinyl}-2,5-dimethyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (21b)

Starting compound: **16c** (0.27 g), reaction time: 8 h, colorless crystals (0.13 g, 33%); **mp**: 135-136 ºC (from acetonitrile); **IR** (KBr): 2967, 1708, 1513, 1432, 1377, 1284, 1221, 1101, 1044, 998, 956, 842 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.00-8.05 (2"'+6"'-H), 7.38-7.42 (3"'+5"'-H), 6.91 (d, *J* = 16.0 Hz, 1H, 2'-H), 6.76 (dd, *J* = 8.0, 16.0 Hz, 1H, 1'-H), 4.88 (d, *J* = 7.2 Hz, 1H, 6a-H), 3.72 (dd, *J* = 7.2, 8.0 Hz, 1H, 3a-H), 3.47 (pseudo t, *J* = 8.0 Hz, 1H, 3-H), 3.08 (s, 3H, N-CH3), 3.00 (m, 1H, CH), 2.71 (s, 3H, N-CH_3), 1.30 (d, *J* = 6.8 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 175.2, 173.2, 162.8, 151.3, 135.0, 131.2, 127.9, 122.1, 120.2, 76.2, 73.5, 53.5, 42.7, 34.2, 25.4, 24.1; **Anal. Calcd** for $C_{19}H_{22}N_6O_3$: C, 59.67; H, 5.80; N, 21.98. Found: C, 59.43; H, 5.82; N, 21.89.

(3*S*,3a*S*,6a*R*)-2-Benzyl-3-{(*E*)-2-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]vinyl}-5-methyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (20c)

Starting compound: **16b** (0.34 g) reaction time: 20.5 h, colorless crystals (0.16 g, 35%); **mp**: 169-173 ºC (from acetonitrile); **IR** (KBr): 1783, 1708, 1492, 1383, 1287, 1140, 1095, 998, 833, 737 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.10 (2"'+6"'-H), 7.58 (3"'+5"'-H), 7.20-7.40 (m, 5H, CH_2Ph), 7.13 (dd, *J* = 9.5, 16.0 Hz, 1H, 1'-H), 6.83 (d, *J* = 16.0 Hz, 1H, 2'-H), 4.92 (d, *J* = 7.0 Hz, 1H, 6a-H), 4.17 (d, *J* = 14.0 Hz, 1H, CH_2), 4.12 (dd, *J* = 1.8, 7.0 Hz, 1H, 3-H), 3.93 (d, *J* = 14.0 Hz, 1H, CH_2), 3.57 (dd, *J* = 1.8, 7.0 Hz, 1H, 3a-H), 3.10 (s, 1H, CH_3); NOE: 3.57/4.92, 6.83, 7.13; 4.12/6.83; **^{13}C NMR** ($CDCl_3$) δ: 175.0 (C=O), 174.1 (C=O), 163.0, 136.0, 135.8, 135.3, 133.6, 130.2, 128.7, 128.6, 127.8, 121.2, 120.9, 75.9 (6a-C), 68.6 (3-C), 57.1 (CH_2), 54.8 (3a-C), 25.4 (CH_3); **Anal. Calcd** for $C_{22}H_{19}N_6O_3Cl$: C, 58.60; H, 4.25; N, 18.64. Found: C, 58.84; H, 4.18; N, 18.73.

(3*R*,3a*S*,6a*R*)-2-Benzyl-3-{(*E*)-2-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]vinyl}-5-methyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (21c)

Starting from **16b** (0.34 g), reaction time: 20.5 h, colorless crystals (0.12 g, 27%); **mp**: 175-176 ºC (from acetonitrile); **IR** (KBr): 1777, 1702, 1498, 1432, 1383, 1287, 1050, 998, 830 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6) δ: 7.52 (2"'+6"'-H), 7.25 (2H, o-Ph), 7.07 (2H, m-Ph), 6.97 (dd, *J* = 8.5, 16.0 Hz, 1H, 1'-H), 6.96 (1H, p-Ph), 6.82 (3"'+5"'-H), 6.71 (d, *J* = 16.0 Hz, 1H, 2'-H), 3.97 (d, *J* = 7.0 Hz, 1H, 6a-H), 3.92 (d, *J* =

15.0 Hz, 1H, CH_2), 3.52 (d, *J* = 15.0 Hz, 1H, CH_2), 3.02 (dd, *J* = 7.0, 8.5 Hz, 1H, 3-H), 2.68 (dd, *J* = 7.0 Hz, 1H, 3a-H), 2.50 (s, 3H, CH_3); NOE 2.68/3.02, 3.97; 3.02/2.68, 6.71, 3.52 (small); 3.97/2.68, 3.52 (medium); 3.52/3.92, 7.25, 3.02(medium); **^{13}C NMR** ($CDCl_3$) δ: 174.8, 173.0, 163.0, 135.9, 135.4, 135.3, 131.9, 130.1, 128.9, 128.5, 127.7, 121.5, 121.3, 76.1 (6a- C), 69.9 (3a-C), 58.6 (3a-C), 53.0 (CH_2), 25.2 (CH_3); **Anal. Calcd** for $C_{22}H_{19}N_6O_3Cl$: C, 58.60; H, 4.25; N, 18.64. Found: C, 58.93; H, 4.16; N, 18.64.

(3*S*,3a*S*,6a*R*)-2-Benzyl-3-{(*E*)-2-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]vinyl}-5-methyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (20d)

Starting from **16d** (0.35 g) reaction time: 7 h, colorless crystals (0.15 g, 33%); **mp**: 112-114 ºC (from acetonitrile); **IR** (KBr): 2949, 1711, 1516, 1438, 1377, 1278, 1134, 1008 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.00 (2”’+6”’-H), 7.40 (3”’+5”’-H), 7.30 (m, 5H, Ph), 7.10 (dd, *J* = 9.0, 16.0 Hz, 1H, 1’-H), 6.81 (d, *J* = 16.0 Hz, 1H, 2’-H), 4.90 (d, *J* = 7.0 Hz, 1H, 6a-H), 4.14 (d, *J* = 14.0 Hz, 1H, CH_2), 4.12 (m, 1H, 3-H), 3.92 (d, *J* = 14.0 Hz, 1H, CH_2), 3.56 (dd, *J* = 2.0, 7.0 Hz, 1H, 3a-H), 3.07 (s, 3H, N-CH_3), 2.99 (m, 1H, CH), 1.30 (d, *J* = 7. 0 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 175.1, 162.7, 151.3, 135.9, 134.9, 133.0, 128.7, 128.6, 127.9, 127.8, 121.3, 120.1, 75.9, 67.7, 57.2, 54.9, 34.1, 25.4, 24.0; **Anal. Calcd** for $C_{25}H_{26}N_6O_3$: C, 65.49; H, 5.72; N, 18.33. Found: C, 65.35; H, 5.62; N, 18.29.

(3*R*,3a*S*,6a*R*)-2-Benzyl-3-{(*E*)-2-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]vinyl}-5-methyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione (21d)

Starting from **16d** (0.35 g), reaction time: 7 h, colorless crystals (0.12 g, 27%); **mp**: 155-156 ºC (from acetonitrile); **IR** (KBr): 2961, 1705, 1516, 1432, 1284, 1047, 1008, 833 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.00 (2”’+6”’-H), 7.40 (3”’+5”’-H), 7.20-7.30 (m, 5H, Ph), 6.90 (d, *J* = 16.0 Hz, 1H, 2’-H), 6.78 (dd, *J* = 8.0, 16.0 Hz, 1H, 1’-H), 4.86 (d, *J* = 7.0 Hz, 1H, 6a-H), 4.26 (d, *J* = 15.0 Hz, 1H, CH_2), 3.86 (d, *J* = 15.0 Hz, 1H, CH_2), 3.70 (m, 2H, 3-H+3a-H), 3.06 (s, 3H, N-CH_3), 2.99 (m, 1H, CH), 1.30 (d, *J* = 7. 0 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 174.9, 173.1, 162.7, 151.2, 135.5, 134.9, 131.3, 128.9, 128.5, 127.8, 127.7, 121.9, 120.2, 76.1, 70.1, 58.6, 53.0, 34.1, 25.3, 24.0; **Anal. Calcd** for $C_{25}H_{26}N_6O_3$: C, 65.49; H, 5.72; N, 18.33. Found: C, 65.56; H, 5.66; N, 18.26.

3-{(*E*)-2-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]vinyl}-2-methyl-2,3-dihydro-1,2-benzisoxazole (19a)

Method A: a solution of anthranilic acid (0.117 g, 0.85 mmol) and trichloroacetic acid (0.02 g) in tetrahydrofuran (10 mL) was cooled to 0 ºC and isopentyl nitrite (0.164 g, 188 µL, 1.40 mmol) was added. The mixture was allowed to warm up to 18-25 ºC, and was stirred at this temperature for 1 h. A solution of **16a** (0.15 g, 0.57 mmol) in tetrahyrofuran (10 mL) was heated up to reflux temperature and the above prepared suspension was added to this solution over 30 min. Intensive gas evolution was observed, and the

mixture was stirred for an additional 1.5 h at reflux temperature. The solvent was evaporated, and the product was purified by flash vacuum chromatography on Kieselgel 60H with dichloromethane as the eluent to give beige crystals (0.042 g, 22%).

Method B: a solution of **16a** (0.17 g, 0.65 mmol) and phenyl[2-(trimethylsilyl)phenyl]iodonium triflate (0.496 g, 0.99 mmol) in dichloromethane (5 mL) was cooled to 0 ºC under an argon atmosphere and 1M solution of tetrabutylammonium fluoride (0.243 g, 0.93 mmol) in tetrahydrofuran (0.93 mL) was added dropwise. The reaction mixture was stirred for 1 h. Water was added to the mixture and extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated. The residue was purified by flash vacuum chromatography on Kieselgel 60H with dichloromethane as the eluent to give beige crystals (0.134 g, 61 %); **mp**: 93 ºC (from acetonitrile); **IR** (KBr): 3099, 1594, 1498, 1459, 1206, 1089, 998, 974, 836, 752 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.04-8.08 (2”’+6”’-H), 7.49-7.54 (3”’+5”’-H), 7.13-7.28 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.97 (pseudo t, *J* = 8.0 Hz, 1H), 6.82-6.90 (m, 2H), 4.86 (d, *J* = 8.0 Hz, 1H), 2.99 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 163.4, 155.8, 136.7, 135.5, 135.1, 129.9, 129.4, 126.3, 124.0, 121.5, 120.9, 117.3, 108.3, 72.9, 46.1; **Anal. Calcd** for $C_{17}H_{14}N_5OCl$: C, 60.09; H, 4.15; N, 20.61. Found: C, 59.85; H, 4.11; N, 20.65.

3-{(*E*)-2-[2-(4-Isopropylphenyl)-2*H*-tetrazol-5-yl]vinyl}-2-methyl-2,3-dihydro-1,2-benzisoxazole (19b)

This compound was prepared by Method B starting from **16c** (0.10 g, 0.37 mmol) to give beige crystalls (0.11 g, 86%); **mp**: 68-69 ºC; **IR** (KBr): 2955, 1597, 1513, 1474, 1459, 1429, 998, 971, 839, 752 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.98-8.03 (2”’+6”’-H), 7.36-7.40 (3”’+5”’-H), 7.19-7.26 (m, 2H), 7.10 (dd, *J* = 6.6, 15.8 Hz, 1H), 7.00 (m, 1H), 6.90 (d, *J* = 12.4 Hz, 1H), 6.86 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 6.6 Hz, 1H), 2.99 (s+m, 4H, CH, N-CH_3), 1.29 (d, *J* = 6.8 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 163.4, 156.2, 151.1, 136.5, 135.1, 129.7, 127.9, 126.8, 124.3, 121.3, 121.9, 120.1, 118.2, 108.6, 73.4, 46.5, 34.2, 24.1; **Anal. Calcd** for $C_{20}H_{21}N_5O$: C, 69.14; H, 6.09; N, 20.16. Found: C, 69.08; H, 6.03; N, 20.14.

2-Benzyl-3-{(*E*)-2-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]vinyl}-2,3-dihydro-1,2-benzisoxazole (19c)

This compound was prepared by Method A starting from **16b** (0.15 g, 0.44 mmol) to give yellow crystals (0.087 g, 48%); **mp**: 138-140 ºC (from acetonitrile); **IR** (KBr): 1597, 1498, 1477, 1459, 1245, 1095, 1008, 980, 824, 752, 659 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 8.02-8.07 (2”’+6”’-H), 7.21-7.53 (m, 10H), 6.74-7.04 (m, 3H), 5.06 (d, *J* = 6.2 Hz, 1H), 4.43 (d, *J* = 13.2 Hz, 1H, CH_2), 4.11 (d, *J* = 13.2 Hz, 1H, CH_2); **^{13}C NMR** ($CDCl_3$) δ: 163.9, 156.5, 137.6, 136.3, 135.9, 135.5, 130.2, 129.8, 129.6, 128.9, 128.2, 126.4, 124.5, 122.0, 121.3, 117.2, 108.9, 70.1, 63.0; **Anal. Calcd** for $C_{23}H_{18}N_5OCl$: C, 66.43; H, 4.36; N, 16.84. Found: C, 66.73; H, 4.35; N, 16.74.

2-Benzyl-3-{(*E*)-2-[2-(4-isopropylphenyl)-2*H*-tetrazol-5-yl]vinyl}-2,3-dihydro-1,2-benzisoxazole (19d)

This compound was prepared by Method B starting from **16d** (0.15 g, 0.43 mmol) to give colorless crystals (0.153 g, 84%); **mp**: 87-88 ºC; **IR** (KBr): 2961, 2859, 1597, 1510, 1474, 1456, 1371, 1239, 1224, 1197, 1002, 836, 749 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.97-8.01 (2"'+6"'-H), 7.21-7.49 (m, 8H), 7.10 (d, *J* = 6.2 Hz, 1H), 6.93-7.04 (m, 2H), 6.86 (d, *J* = 9.2 Hz, 1H), 6.79 (d, *J* = 15.8 Hz, 1H), 5.05 (d, *J* = 6.2 Hz, 1H), 4.41 (d, *J* = 13.0 Hz, 1H, CH_2), 4.11 (d, *J* = 13.0 Hz, 1H, CH_2), 2.98 (m, 1H, CH), 1.28 (d, *J* = 6.6 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 163.5, 156.5, 151.1, 137.0, 136.3, 135.1, 129.7, 129.6, 128.9, 128.1, 127.9, 126.5, 124.5, 121..9, 120.1, 117.6, 108.8, 70.2, 62.9, 34.2, 24.1; **Anal. Calcd** for $C_{26}H_{25}N_5O$: C, 73.74; H, 5.95; N, 16.54. Found: C, 73.62; H, 5.97; N, 16.50.

ACKNOWLEDGEMENTS

Thanks are due to financial support provided by OTKA T 47317, 1/047 NKFP MediChem, COST B16 as well as the QLK2-CT-2002-90436 project funded by the European Union for Center of Excellence in Biomolecular Chemistry.

REFERENCES

1. G. Timári, Gy. Hajós, A. Messmer, and A. Gelléri, *Monatshefte,* 1988, **119**, 1037.
2. A. Messmer, Gy. Hajós, and G. Timári, *Monatshefte*, 1988, **119**, 1113.
3. A. Messmer, Gy. Hajós, G. Timári, and A. Gelléri, *Monatshefte*, 1988, **119**, 1121.
4. Zs. Riedl, Gy. Hajós, P. Kövér, and G. Kollenz, *Arkivoc*, 2003, **v**, 62.
5. A. Kotschy, Gy. Hajós, G. Timári, and A. Messmer, *J. Org. Chem*., 1996, **61**, 4423.
6. A. Messmer, Gy. Hajós, and G. Timári, *Tetrahedron*, 1992, **48**, 8451.
7. I. Nagy, D. Kónya, Zs. Riedl, A. Kotschy, G. Timári, A. Messmer, and Gy. Hajós, *Tetrahedron*, 2003, **59**, 7485.
8. W. Lehnert, *Tetrahedron*, 1972, **28**, 663.
9. I. Matsuda, S. Murata, and Y. Ishii, *J. Chem. Soc., Perkin Trans. 1*, 1979, 26.
10. S. Park and R. J. Kazlauskas, *J. Org. Chem.*, 2001, **66**, 8395.
11. S. Chun, S. V. Dzyuba, and R. A. Bartsch, *Anal. Chem.*, 2001, **73**, 3737.
12. T. Kitamura, M. Yamane, K. Inoue, M. Todaka, N. Fukatsu, Z. Meng, and Y. Fujiwara, *J. Am. Chem. Soc.*, 1999, **121**, 11674.
13. T. Thiemann, H. Fujii, D. Ohira, K. Arima, Y. Li, and S. Mataka, *New J. Chem.*, 2003, **27**, 1377.