π-FACIAL SELECTIVITY IN 1,3-DIPOLAR CYCLOADDITION REACTIONS OF α-METHYLIDENE-γ-LACTONE SUBSTITUTED BY 4-METHYL-2,6,7-TRIOXABICYCLO[2.2.2]OCTAN-1-YL GROUP IN γ-POSITION

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Dedicated to Professor Jaroslav Jonas on the occasion of his 65th birthday.

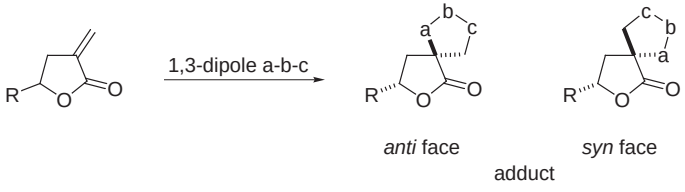
Diastereoselectivity of 1,3-dipolar cycloaddition reactions of benzyl azide, diazomethane, a nitrile oxide and a nitrile imine to α-methylidene-γ-lactone dipolarophile was effectively controlled by a bulky γ-substituent, 4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl in γ-position of the dipolarophile. The dipoles added from the less hindered face of the double bond with an excellent selectivity. Enantiomerically pure dipolarophile was prepared from the easily available (*S*)-5-oxotetrahydrohydrofuran-2-carboxylic acid.

Keywords: 1,3-Dipolar cycloadditions; Methylene lactones; Stereoselective synthesis; Spiro compounds; Orthoesters.

1,3-Dipolar cycloaddition reactions have acquired high reputation in the field of organic synthesis, becoming probably the most frequently used tool for construction of five-membered heterocycles[1]. While various examples of 1,3-dipolar cycloadditions have been known for nearly a century, the recent work focused mainly on the regioselectivity and stereoselectivity of the reaction benefits from the reaction mechanism concept that has been developing from the 1960's (refs[1,2]). Among the number of dipolarophiles suitable for 1,3-dipolar cycloaddition reaction, the α-methylidenelactone moiety appeared first in scattered examples of the reactions of diazomethane with some naturally occurring sesquiterpene lactones[3]. Later on, numerous spiropyrazoline adducts were also prepared in the course of methylenation of exomethylidene double bond in the preparation of cyclopropyl analogues of the sesquiterpene lactones[4]. In 1990's, the reac-

tions of methylidenelactones with other basic classes of 1,3-dipolar compounds have been studied in more or less detail[5].

In the last decade, a couple of papers also appeared dealing with stereoselective cycloadditions of various dipolar compounds on substituted α-methylidene-γ-lactones. Savage with coworkers studied π-facial selectivity of the dipole approach to the exomethylidene double bond in α-position. The selectivity was controlled by the bulkiness of the substituent in γ-position of the lactone[6]. The dipoles preferred addition to the less hindered face of the double bond, which was *anti* to the γ-substituent, forming diastereoselectively corresponding spiro heterocycles (Scheme 1). Very good results have been achieved with 2,3-dichlorophenyl as well as *tert*-butyl derivatives (Table I).



SCHEME 1

TABLE I

Some examples of stereoselective 1,3-dipolar cycloadditions of γ-substituted α-methylidene-γ-lactones

γ-Substituent	Dipole	*anti* face adduct, %	*syn* face adduct, %	Ref.
Methyl	Propionitrile oxide	81	19	6a
Methyl	Benzonitrile *N*-methyl imine	75	25	6b
tert-Butyl	Propionitrile oxide	90	10	6a
tert-Butyl	Benzonitrile *N*-methyl imine	100[a]	–[a]	6b
Phenyl	Propionitrile oxide	89	11	6a
2-Methoxyphenyl	Propionitrile oxide	82	18	6a
2,6-Dichlorophenyl	Propionitrile oxide	100[a]	–[a]	6a
2,6-Dichlorophenyl	Benzonitrile *N*-methyl imine	100[a]	–[a]	6b

[a] The *syn*-addition product could not be detected by ^{1}H NMR or HPLC.

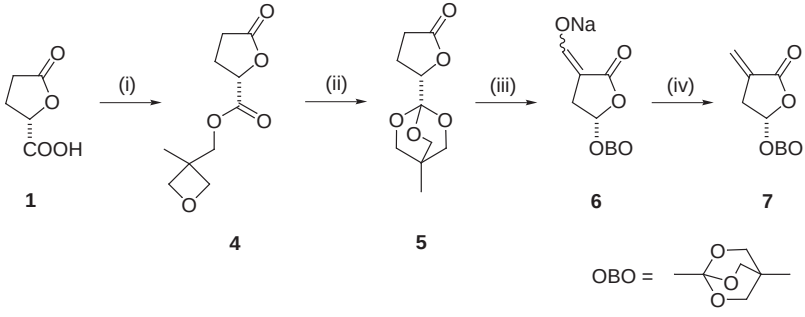
The results have undoubtedly proven that this mode of substitution gave rise to a significant siteselective effect on the addition of even small dipolar compounds. But the most effective substituents offered only a limited potential in further synthetic utilization. An effort to synthesize an α-methylidenelactone dipolarophile substituted in γ-position with bulky group that would combine satisfactory face selectivity control with a high synthetic potential, was the primary motivation of our work.

Seeking a suitableγ-substituted system, our attention was attracted by (*S*)-5-oxotetrahydrofuran-2-carboxylic acid (**1**) that is easily accessible from L-glutamic acid[7], an inexpensive member of a chiral pool of natural products. The carboxy group in γ-position of the corresponding methylidenelactone would undoubtedly offer various ways of further synthetic utilization with an advantage of possible preparation of chiral derivatives. However, previously reported cycloadditions of such dipolarophiles with alkoxycarbonyl group in γ-position of the lactone ring did not run with the desired selectivity. For instance, the reactions of methyl 4-(cyanomethylidene)-5-oxotetrahydrofuran-2-carboxylate with various nitrile oxides ran with only moderate diastereomeric excess that did not exceed 34% (ref.[8]).

To increase the π-facial diastereoselectivity of the reaction, we decided to transform the γ-carboxy group of the dipolarophile into its orthoester derivative. Orthoesters are commonly used as protecting groups shielding the carbonyl group of carboxylic functionality against nucleophilic attack or metal hydride reduction[9]. Therefore, the orthoester is not only bulky enough to fulfill the steric requirements, but it can also protect the carboxyl in the introduction of exomethylidene double bond into the α-position. Moreover, this kind of protection facilitates retention of the γ-carbon configuration in the synthesis preventing racemization due to proton abstraction in this position.

In preparation of the desired dipolarophile, we followed the reaction (Scheme 2) using the Corey and Raju protocol[10] for protection of carboxyl as a 4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl (OBO) orthoester group. The carbonyl chloride **2** was prepared by refluxing **1** with an excess of thionyl chloride[11] and subsequently reacted with a 3-(hydroxymethyl)-3-methyloxetane (**3**). The resulting ester **4** gave orthoester **5** in a moderate yield by the reaction catalyzed with boron trifluoride etherate. The original procedure[10] was slightly modified using hexamethylenetetramine instead of commonly used triethylamine. The reason was to remove the catalyst from the crude product as thoroughly as possible, since even traces of acids would destroy the OBO group after exposure to atmospheric humidity. Exomethylidene group was then introduced by the Murray method[12]. So-

dium salt **6**, prepared by the Claisen condensation of OBO lactone **5** with ethyl formate, was reduced with paraformaldehyde in refluxing THF yielding methylidenelactone **7** in about 60% yield with more than 98% e.e. as detected by enantioselective HPLC.



(i) 1. $SOCl_2$, 2. pyridine, (3-methyloxetan-3-yl)methanol; (ii) 1. $BF_3 \cdot Et_2O$, 2. hexamethylenetetramine; (iii) Na, ethyl formate/toluene, 110 °C; (iv) $(CH_2O)_n$/THF, 70 °C

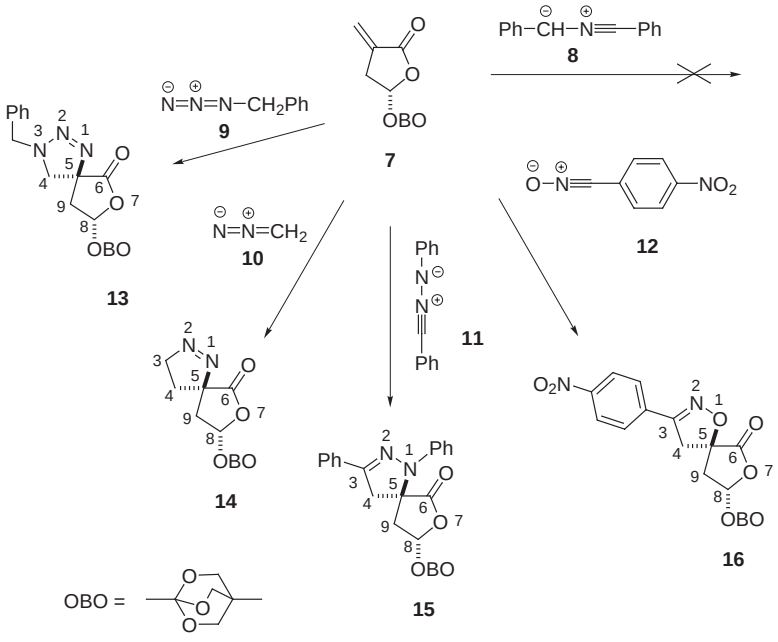
SCHEME 2

Reactivity of the methylidenelactone **7** in 1,3-dipolar cycloaddition reactions with a set of propargyl/allenyl anion type dipoles, **8**–**12**, was then studied with careful respect to their diastereoselectivity. The nitrile ylide **8**, photochemically generated from 2,3-diphenyl-2*H*-azirine, failed to react with **7** most probably due to a facile polymerization of methylidenelactone initiated by irradiation (*cf.* ref.[13]).

The other 1,3-dipolar compounds, benzyl azide (**9**), diazomethane (**10**), nitrile imine **11**, and nitrile oxide **12**, gave, however, the corresponding spirolactones **13**–**16**. As proven by NMR spectra (NOESY of **13**, H,H COSY of **14**, and HMBC of **15** and **16**), the dipolar compounds add lactone **7** with the regioselectivity previously described in the literature[5,14]. Moreover, in agreement with our assumption, the spirotriazoline **13**, spiropyrazolines **14**, **15** and spiroisoxazoline **16** were formed with an outstanding diastereoselectivity reflecting indeed the approach of the dipoles from the less hindered "face" of the exomethylidene double bond of **7** (Scheme 3). Steric requirements of the OBO orthoester group are clearly illustrated on an ORTEP picture of **7** obtained after its X-ray analysis (Fig. 1).

In order to perceive the stereochemistry of adducts, ^{1}H NMR spectra of crude products were measured in all cycloadditions. Significant differences between the diastereomers resulting from cycloadditions to different faces of dipolarophile were expected in the chemical shifts of γ-protons (H-8) of lactone rings. Such differences were indeed detected in less selective

cycloadditions of other γ-substituted methylidenelactones[6,8]. Contrary to the benzyl azide and nitrile oxide reactions, small amounts (less than 5%) of byproducts with spectroscopic patterns resembling the diastereomers arising from attack to the face of double bond *syn* to the OBO substituent were detected in the cycloadditions of diazomethane and nitrile imine. Al-



SCHEME 3

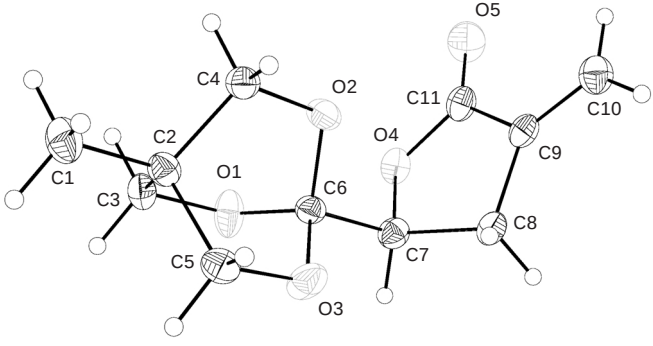


FIG. 1
ORTEP drawing of compound **7**

though we were not able to isolate these compounds for identification, we assume the formation of these cycloadducts rather than regioisomers, because the regioselectivity of the cycloadditions has been demonstrated in numerous examples[5].

The configuration of the isolated adducts **13**–**16** was determined by NOESY NMR spectra, where no significant interactions were found between H-8 and the methylene protons H-4 originating from the lactone exomethylidene. On the other hand, positive NOE interactions between H-4β and H-9β were detected in NOESY spectra of the all cycloadducts. Assignment of the H-9 signal with the lower $^3J(8,9)$ coupling constant to the H-9β proton that is located *trans* to the H-8, was confirmed by NOESY spectrum of the nitrile imine adduct **15** where protons in *ortho*-position of *N*-phenyl substituent in pyrrazole ring interacted with the protons H-8 and H-9α, both located on the same side of the lactone ring (Fig. 2).

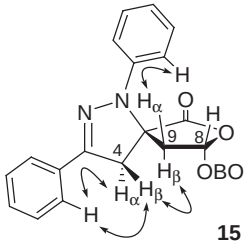


FIG. 2
NOE interactions in compound **15**

In conclusion, we have found that protection of carboxylic function of (*S*)-5-oxotetrahydrofuran-2-carboxylic acid (**1**) by a bulky orthoester (OBO) group not only allowed preparation of corresponding methylidenelactone **7** by a standard condensation procedure, but significantly improved the diastereoselectivity of 1,3-dipolar cycloaddition reactions of **7** with dipoles of the propargyl/alllenyl anion type, such as benzyl azide, diazomethane, nitrile oxide **11** and nitrile imine **12**. The dipoles approached the exomethylidene double bond of **7** from the less hindered face forming the corresponding spiro heterocycles.

EXPERIMENTAL

Melting points were obtained on a Kofler block and are uncorrected. Optical rotations were determined on a JASCO DIP-370 digital polarimeter ($[\alpha]_D^{20}$ are given in 10^{-1} deg cm^2 g^{-1}). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz

for ^{13}C) and a Bruker Avance 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C) spectrometers in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants *J* in Hz. Ultraviolet spectra were recorded on a UV-VIS spectrophotometer UV-101 Shimadzu. IR spectra (wavenumbers in cm^{-1}) were measured in KBr pellets on a Genesis series FTIR, ATI Matson spectrometer. Elemental analyses were performed by analytical laboratory of Lachema Brno. Enantioselective HPLC separations were performed on a Shimadzu 10A instrument with Jasco CD-1595 detector using Chiralpak® AD column. Literature procedures were used for preparations of (*S*)-5-oxotetrahydrofuran-2-carboxylic acid[7b] (**1**), acyl chloride[11] **2**, (3-methyloxetan-3-yl)methanol[15], benzyl azide[16], diazomethane[17], 4-nitrobenzohydroximoyl chloride[18], and *N*-phenylbenzohydrazonoyl chloride[19].

(3-Methyloxetan-3-yl)methyl (*S*)-5-Oxotetrahydrofuran-2-carboxylate (**4**)

Acyl chloride **2** (28.223 g, 190 mmol) was added dropwise to a mixture of (3-methyloxetan-3-yl)methanol (19.014 g, 186 mmol), dry pyridine (16 ml, 200 mmol), and dry dichloromethane (50 ml) stirred in an ice bath under argon atmosphere. The pyridinium chloride precipitated after 30 min of additional stirring at the same temperature was removed by filtration. The filtrate was washed with water (3 × 30 ml) and extracted with dichloromethane (2 × 30 ml), and then the aqueous washings were extracted with dichloromethane containing a small amount of pyridine. Combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuum yielding ester **4** (33.006 g, 83%) as a white solid. M.p. 35–40 °C; $[\alpha]_D^{20}$ +6.4 (*c* 2, $CHCl_3$). For $C_{10}H_{14}O_5$ (214.2) calculated: 56.07% C, 6.59% H; found: 56.32% C, 6.72% H. IR (KBr): 2 966, 2 875, 1 792, 1 747, 1 689, 1 220, 1 146, 1 070, 980. ^{1}H NMR (300 MHz): 4.99 dd, 1 H, *J*(4α,5) = 8.3, *J*(4β,5) = 4.6 (H-5); 4.49 d, 2 H, *J* = 4.9 (H-2′α, H-4′α); 4.41 d, 2 H, *J* = 5.9 (H-2′β, H-4′β); 4.37 and 4.33 AB-system, 2 H, *J*(AB) = 12.7 (CCH_2O); 2.60 m, 3 H (2 × H-3, H-4α); 2.36 m, 1 H (H-4β); 1.34 s, 3 H (CH_3). ^{13}C NMR (75 MHz): 175.9, 170.0, 79.3, 75.7, 69.8, 26.7, 39.3, 26.0, 21.0.

(*S*)-5-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)tetrahydrofuran-2-one (**5**)

Boron trifluoride diethyl etherate (0.15 ml, 1.2 mmol) was added dropwise to a dichloromethane solution (30 ml) of ester **4** (4.990 g, 23.3 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for another 3 h. A subsequent addition of a dichloromethane solution (15 ml) of hexamethylenetetramine (0.166 g, 1.2 mmol) gave a suspension which was filtered through a thin alumina pad. The filtrate was concentrated in vacuum giving the crude OBO lactone **5** which was recrystallized from ethyl acetate (3.092 g, 62%). M.p. 127–130 °C (ethyl acetate); $[\alpha]_D^{20}$ +10.9 (*c* 1, $CHCl_3$). For $C_{10}H_{14}O_5$ (214.2) calculated: 56.07% C, 6.59% H; found: 56.28% C, 6.22% H. IR (KBr): 2 966, 2 943, 2 883, 1 778, 1 155, 1 055, 1 016, 991, 870. ^{1}H NMR (300 MHz): 4.43 dd, 1 H, *J*(4α,5) = 8.5, *J*(4β,5) = 3.5 (H-5); 3.94 s, 6 H (6 × H-3′); 2.68–2.55 m, 1 H (H-3α); 2.42–2.31 m, 2 H (H-3β, H-4α); 2.26–2.16 m, 1 H (H-4β); 0.82 s, 3 H (CH_3). ^{13}C NMR (75 MHz): 177.6, 108.1, 79.1, 73.2, 31.4, 27.6, 22.7, 14.7.

(*S*)-3-Methylidene-5-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)dihydrofuran-2-one (**7**)

To a fine suspension of sodium (1.225 g, 53.3 mmol) in dry toluene (40 ml), a mixture of lactone **5** (11.419 g, 53.3 mmol) and ethyl formate (4.69 ml, 58 mmol) in dry toluene (50 ml) was added dropwise under argon atmosphere. The reaction mixture was stirred at ambient temperature for 12 h and then diluted with dry diethyl ether (40 ml). The resulting suspension was filtered off and dried to give a crude sodium salt **6** (13.792 g, 98%) which was used in subsequent syntheses without further purification. In one of such reactions, the crude **6** (1.051 g, 4 mmol) was suspended in dry THF (20 ml) together with paraformaldehyde (0.24 g, 8 mmol) and refluxed under argon atmosphere for 3 h. Then, the reaction mixture was allowed to chill to ambient temperature and stirred for another 12 h, and then filtered through a cellite pad. The filtrate was dried over anhydrous $CaCl_2$ and concentrated in vacuum yielding the methylidenelactone **7** (0.503 g, 56%) as a white solid. M.p. 189–191 °C; $[\alpha]_D^{20}$ +44.9 (*c* 0.9, $CHCl_3$). For $C_{11}H_{14}O_5$ (226.2) calculated: 58.40% C, 6.24% H; found: 58.52% C, 6.18% H. IR (KBr): 2 940, 2 885, 1 770, 1 402, 1 323, 1 252, 1 169, 1 109, 1 051, 1 024, 960, 820, 688. ^{1}H NMR (300 MHz): 6.20 t, 1 H, *J* = 3.0 ((*Z*)-HC=); 5.60 t, 1 H, *J* = 2.6 ((*E*)-HC=); 3.93 s, 6 H (6 × H-3′); 4.45 dd, 1 H, *J*(4α,5) = 8.9, *J*(4β,5) = 4.3 (H-5); 3.07 tdd, 1 H, ^4J = 2.6, *J*(4α,4β) = 17.8, *J*(4β,5) = 4.3 (H-4β); 2.87 tdd, 1 H, ^4J = 3.0, *J*(4α,4β) = 17.8, *J*(4α,5) = 8.9 (H-4α); 0.82 s, 3 H (CH_3). ^{13}C NMR (75 MHz): 170.0, 133.8, 121.6, 107.6, 75.7, 72.3, 31.3, 28.4, 14.5.

(5*S*,8*S*)-3-Benzyl-8-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-7-oxa-1,2,3-triazaspiro[4.4]non-1-en-6-one (**13**)

A solution of methylidenelactone **7** (200 mg, 0.89 mmol) in benzyl azide (1.2 ml, 8.8 mmol) was stirred at 60 °C for 3 days until no starting **7** could be detected by TLC. After removing excess benzyl azide in vacuum, a sufficiently pure spirotriazoline **13** was obtained (306 mg, 96%). An analytical sample was recrystallized from diethyl ether–ethyl acetate as colorless crystals. M.p. 161–164 °C; $[\alpha]_D^{20}$ +236.3 (*c* 0.8, $CHCl_3$). For $C_{18}H_{21}N_3O_5$ (359.4) calculated: 60.16% C, 5.89% H, 11.69% N; found: 60.29% C, 5.73% H, 11.47% N. IR (KBr): 2 964, 2 893, 1 784, 1 641, 1 446, 1 358, 1 329, 1 284, 1 228, 1 203, 1 120, 1 153, 1 076, 1 049, 1 009, 1 001, 941, 742, 700, 644. ^{1}H NMR (300 MHz): 7.25–7.40 m, 5 H (H-Ar); 4.96 d, 1 H, *J*(a,b) = 15.2 (C**H**$_a$H$_b$Ph); 4.74 d, 1 H, *J*(a,b) = 15.2 (C**H**$_a$H$_b$Ph); 4.66 dd, 1 H, *J*(8,9α) = 7.9, *J*(8,9β) = 5.6 (H-8); 3.91 s, 6 H (6 × H-3′); 3.46 d, *J*(4α,4β) = 10.6 (H-4α); 3.07 d, *J*(4α,4β) = 10.6 (H-4β); 2.67 dd, *J*(9α,9β) = 14.2, *J*(8,9α) = 7.9 (H-9α); 2.32 dd, *J*(9α,9β) = 14.2, *J*(8,9β) = 5.6 (H-9β); 0.81 s, 3 H (CH_3). ^{13}C NMR (75.47 MHz): 173.7; 135.2; 128.9; 128.1 (2 × CH); 106.9; 82.5; 76.5; 72.7; 54.0; 52.9; 34.9; 31.0; 14.2.

(5*R*,8*S*)-8-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-7-oxa-1,2-diazaspiro[4.4]non-1-en-6-one (**14**)

To a suspension of lactone **7** (98 mg, 0.44 mmol) in dry benzene (5 ml), an ethereal solution of diazomethane was added of a concentration that gives a permanent yellow color of the reaction mixture. After 5 h the reaction mixture was concentrated in vacuum. The residue was recrystallized from ethyl acetate–heptane (2 : 1) to give colorless crystals of the adduct **14** (42 mg, 36%). M.p. 133–136 °C; $[\alpha]_D^{20}$ +321.8 (*c* 1, $CHCl_3$). For $C_{12}H_{16}N_2O_5$ (268.3) calculated: 53.73% C, 6.01% H, 10.44% N; found: 53.96% C, 5.78% H, 10.38% N. IR (KBr): 2 947, 2 889, 1 782, 1 637, 1 458, 1 282, 1 194, 1 142, 1 051, 1 005, 891. ^{1}H NMR (300 MHz):

4.85 dd, 1 H, *J*(8,9α) = 8.3, *J*(8,9β) = 6.0 (H-8); 4.72–4.65 m, 2 H (H-3); 3.97 s, 6 H (6 × H-3′); 2.80 dd, 1 H, *J*(8,9α) = 8.3, *J*(9α,9β) = 14.2 (H-9α); 2.45 dd, 1 H, *J*(8,9β) = 6.0, *J*(9α,9β) = 14.2 (H-9β); 2.31–2.25 m, 1 H (H-4α); 1.63–1.55 m, 1 H (H-4β); 0.85 s, 3 H (CH_3). ^{13}C NMR (75 MHz): 173.5, 107.5, 94.5, 78.6, 77.6, 73.2, 33.9, 31.5, 27.9, 14.7.

(5*R*,8*S*)-8-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-1,3-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-2-en-6-one (**15**)

A solution of methylidenelactone **7** (177 mg, 0.78 mmol), *N*-phenylbenzohydrazonoyl chloride (360 mg, 1.56 mmol), and triethylamine (0.22 ml, 1.56 mmol) in benzene (5 ml) was stirred at room temperature for 12 h. Triethylamine hydrochloride was filtered off, the filtrate was washed with water and dried over anhydrous magnesium sulfate. The solid residue resulting after evaporation of the solvent was chromatographed on silica gel. After benzene elution of a byproduct resulting from an excess of 1,3-dipolar compound, the spiropyrazoline **15** was eluted with diethyl ether as yellowish oil (262 mg) which crystallized upon standing. Recrystallization from diethyl ether gave **15** as yellowish crystals (120 mg, 37%). M.p. 117–119 °C; $[\alpha]_D^{20}$ +79.2 (*c* 0.7, $CHCl_3$). For $C_{24}H_{24}N_2O_5$ (420.5) calculated: 68.56% C, 5.75% H, 6.66% N; found: 68.72% C, 5.46% H, 6.53% N. IR (KBr): 3 060, 2 960, 2 883, 1 786, 1 597, 1 495, 1 388, 1 174, 1 101, 1 049, 1 024, 943, 754, 690. ^{1}H NMR (600 MHz): 7.71 d, 2 H, *J* = 8.2 (H-Ar); 7.40 t, 2 H, *J* = 7.6 (H-Ar); 7.34 m, 1 H (H-Ar); 7.28 t, 2 H, *J* = 8.6 (H-Ar); 7.11 d, 2 H, *J* = 7.6 (H-Ar); 6.95 t, 1 H, *J* = 7.3 (H-Ar); 4.50 dd, 1 H, *J*(8,9α) = 9.9, *J*(8,9β) = 3.6 (H-8); 3.98 s, 6 H (6 × H-3′); 3.84 d, 1 H, *J*(4α,4β) = 17.2 (H-4α); 3.33 d, 1 H, *J*(4α,4β) = 17.2 (H-4β); 2.70 dd, 1 H, *J*(8,9α) = 9.9, *J*(9α,9β) = 14.9 (H-9α); 2.43 dd, 1 H, *J*(8,9β) = 3.6, *J*(9α,9β) = 14.9 (H-9β); 0.86 s, 3 H (CH_3). ^{13}C NMR (150 MHz): 176.8, 146.7, 142.8, 132.1, 129.4, 129.0, 128.6, 125.9, 121.5, 116.1, 107.2, 76.2, 72.8, 69.5, 48.7, 45.8, 32.0, 14.2.

(5*R*,8*S*)-8-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-(4-nitrophenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-en-6-one (**16**)

A solution of 4-nitrobenzohydroximoyl chloride (559 mg, 2.78 mmol) in dry benzene (30 ml) was added dropwise to a mixture of lactone **7** (315 mg, 1.39 mmol) and triethylamine (0.4 ml, 2.87 mmol) in dry benzene (10 ml). The reaction mixture was stirred under argon atmosphere for 2 days, then washed with water (3 × 15 ml). The aqueous layer was extracted with dichloromethane (3 × 15 ml) which contained a small amount of triethylamine. Combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuum. The residue was washed with hot methanol to give adduct **16** (369 mg, 68%) as a satisfactorily pure, yellowish solid. M.p. 263–270 °C; $[\alpha]_D^{20}$ +149.1 (*c* 0.7, DMSO). For $C_{18}H_{18}N_2O_8$ (268.3) calculated: 55.39% C, 4.65% H, 7.18% N; found: 55.51% C, 4.72% H, 7.34% N. IR (KBr): 2 966, 2 897, 1 786, 1 518, 1 348, 1 265, 1 192, 1 072, 1 041, 1 001, 918, 852, 750. ^{1}H NMR (300 MHz): 8.28 d, 2 H, *J* = 8.9 (H-Ar); 7.82 d, 2 H, *J* = 8.9 (H-Ar); 4.62 dd, 1 H, *J*(8,9α) = 7.9, *J*(8,9β) = 5.3 (H-8); 3.98 s, 6 H (6 × H-3′); 3.89 d, 1 H, *J*(4α,4β) = 17.2 (H-4α); 3.45 d, 1 H, *J*(4α,4β) = 17.2 (H-4β); 2.76 dd, 1 H, *J*(8,9α) = 7.9, *J*(9α,9β) = 14.6 (H-9α); 2.66 d, 2 H, *J*(8,9β) = 5.3, *J*(9α,9β) = 14.6 (H-9β); 0.86 s, 3 H (CH_3). ^{13}C NMR (75 MHz): 174.2, 155.6, 148.3, 134.3, 128.1, 124.0, 106.4, 85.7, 76.0, 71.9, 43.1, 34.9, 30.5, 13.4.

X-Ray Structural Analysis

Crystals of methylidenelactone **7** suitable for X-ray analysis were obtained by careful recrystallization from diethyl ether–methanol (2 : 1). The intensity data were collected on a KUMA KM-4 CCD kappa-axis diffractometer using a graphite monochromatized MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods. Non-hydrogen atoms were refined anisotropically while hydrogen atoms were inserted in calculated positions and isotropically refined assuming a "ride-on" model. The crystal data for compound **7** and other pertinent information are summarized in Table II. The programs used were: SHELX97

TABLE II
Crystallographic parameters, data collection and refinement for methylidenelactone **7**

Empirical formula	$C_{11}H_{14}O_5$
Formula weight	226.22
Temperature, K	120(2)
Wavelength, Å	0.71073
Crystal system; space group	orthorhombic, $P2_12_12_1$
a, Å	9.566(1)
b, Å	9.789(1)
c, Å	11.189(1)
α, °	90
β, °	90
γ, °	90
Volume, Å^3; *Z*	1 047.8(4); 4
Calculated density, g cm^{-3}	1.434
Absorption coefficient, mm^{-1}	0.114
F(000)	480
Crystal size, mm	0.37 × 0.37 × 0.26
θ range for data collection, °	3.49 to 27.50
Range of *hkl*	–12→10, –12→12, –14→14
Reflections collected	8 405
Independent reflections	2 342 (R_{int} = 0.0260)
Completeness, % (to 2θ = 27.50)	98.0
Max. and min. transmission	0.9710 and 0.9592
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	2 342/0/145
Goodness-of-fit on F^2	1.072
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0268, wR_2 = 0.0661
R indices (all data)	R_1 = 0.0284, wR_2 = 0.0672
Absolute structure parameter	0.3(7)
Largest difference peak and hole, e Å^{-3}	0.173 and –0.174

program package[20] for the structure determination and structure refinement, and XP program of Bruker SHELXTL V 5.1 program package[21] for drawings (Fig. 1). CCDC 178635 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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REFERENCES

1. a) Gothelf K. V., Jorgensen K. A.: *Chem. Rev. (Washington, D. C.)* **1998**, *98*, 863; b) Dell C. P.: *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873; c) Padwa A. in: *Comprehensive Organic Synthesis* (B. H. Trost and W. Flemming, Eds), Vol. 4, p. 1069. Pergamon Press, Oxford 1991; d) Padwa A. (Ed.): *1,3-Dipolar Cycloaddition Chemistry*. John Wiley & Sons, New York 1984; e) Huisgen R.: *Angew. Chem.* **1963**, *75*, 604.
2. a) Woodward R. B., Hoffmann R.: *J. Am. Chem. Soc.* **1965**, *87*, 395; b) Houk K. N., Yamaguchi K. in: *1,3-Dipolar Cycloaddition Chemistry* (A. Padwa, Ed.), Vol. 2, p. 407. Wiley, New York 1984.
3. For some early examples see a) Deuel P. G., Geissman T. A.: *J. Am. Chem. Soc.* **1957**, *79*, 3778; b) Dolejš L., Herout V., Šorm F.: *Collect. Czech. Chem. Commun.* **1958**, 23, 504; c) Herz W., Hoegenauer G.: *J. Org. Chem.* **1962**, *27*, 905.
4. a) Kalsi P. S., Vij V. K., Singh O. S., Wadia M. S.: *Phytochemistry* **1977**, *16*, 784; b) Appendino G., Ghilardi E., Cravotto G., Gariboldi P.: *Collect. Czech. Chem. Commun.* **1991**, *56*, 1052; and references therein.
5. a) Jonas J., Głowiak T., Žák Z., Trška P., Mazal C.: *Collect. Czech. Chem. Commun.* **1991**, *56*, 973; b) Otto A., Ziemer B., Liebscher J.: *Synthesis* **1999**, 965; c) Štverková S., Žák Z., Jonas J.: *Liebigs Ann. Chem.* **1993**, 1169; d) Micúch P., Fišera L., Ondruš V., Ertl P.: *Molecules* **1997**, *2*, 57; e) Štverková S., Žák Z., Jonas J.: *Liebigs Ann. Chem.* **1995**, 477; f) de March P., Figueredo M., Font J.: *Heterocycles* **1999**, *50*, 1213; g) de March P., el Arrad M., Figueredo M., Font J.: *Tetrahedron* **1998**, *54*, 11613; h) Častulík J., Jonas J., Mazal C.: *Collect. Czech. Chem. Commun.* **2000**, *65*, 708; i) Častulík J., Marek J., Mazal C.: *Tetrahedron* **2001**, *57*, 8339.
6. a) Pereira S. M., Savage G. P., Simpson G. W., Greenwood R. J., Mackay M. F.: *Aust. J. Chem.* **1993**, *46*, 1401; b) Dunstan J. B. F., Elsey G. M., Russell R. A., Savage G. P., Simpson G. W., Tiekink E. R. T.: *Aust. J. Chem.* **1998**, *51*, 499.
7. a) Červinka O., Hub L.: *Collect. Czech. Chem. Commun.* **1968**, *33*, 2927; b) Gringore O. H., Rouessac F. P.: *Org. Synth.* **1984**, *63*, 121.
8. Pirc S., Golič-Grdadolnik S., Svete J., Stanovnik B.: *8th Blue Danube Symposium on Heterocyclic Chemistry, Bled (Slovenia), September 24–27, 2000*. Abstract of Papers, p. 122.
9. Kocieński P. J.: *Protecting Groups*, p. 145. Thieme, Stuttgart–New York 1994.
10. Corey E. J., Raju N.: *Tetrahedron Lett.* **1983**, *24*, 5571.
11. Marquart A. L., Podlogar B. L., Huber E. W., Demeter D. A., Peet N. P., Weintraub H. J. R., Angelastro M. R.: *J. Org. Chem.* **1994**, *59*, 2092.
12. Murray A. W., Reid R. G.: *J. Chem. Soc., Chem. Commun.* **1984**, 132.

13. Stansbury J. W., Antonucci J. M.: *Dent. Mater.* **1992**, *8*, 270.
14. Alonso-Perarnau D., de March P., Figueredo M., Font J.: *An. Quim.* **1994**, *90*, 473.
15. Rakus K., Verevkin S. G., Peng W.-H., Beckhaus H.-D., Ruechardt C.: *Liebigs Ann.* **1995**, 2059.
16. Juranić I., Husinec S., Savić V., Porter A. E. A.: *Collect. Czech. Chem. Commun.* **1991**, *56*, 411.
17. Arndt F.: *Org. Synth., Coll. Vol. 2*, **1946**, 165.
18. Hegarty A. F., Mullane M.: *J. Chem. Soc., Perkin Trans. 2* **1986**, 995.
19. Huisgen R., Seidel M., Wallbillich G.: *Tetrahedron* **1962**, *17*, 3.
20. Sheldrick G. M.: *SHELX97 Program Package*. University of Goettingen, Goettingen 1997.
21. Sheldrick G. M.: *SHELXTL V 5.1*. Bruker AXS GmbH, Karlsruhe 1998.