1,3-Dipolar cycloadditions of D-erythrose- and D-threose-derived nitrones to maleimides

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To Fritz Sauter on the occasion of his 70th birthday
(received 10 Nov 00; accepted 30 Oct 01; published on the web 07 Nov 01)

Abstract
The nitrones derived from cyclic acetals of D-erythrose 1a,b and D-threose 2a,b react with N-phenylmaleimide (3) to afford the corresponding diastereomeric isoxazolidines. The stereoselectivity is dependent on the steric hindrance of the nitrone. In the case of D-erythro-derived nitrones 1a,b the cycloaddition is exo-selective. The major products are in the C-3/C-4 erythro- and C-3/C-3a trans-configuration. This finding can be rationalized by a less hindered exo-attack of the (Z)-nitrone in an antiperiplanar manner with respect to the largest group of the cyclic acetal. The cycloaddition to the chiral maleimides 12 and 13 is less stereoselective.

Keywords: Cycloaddition, nitrones, microwave heating, isoxazolidines, maleimides

Introduction
The nitrone – olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centers in a single step. Based on an evaluation of the nitrone cycloaddition, it was felt that the configuration of these new centers could be influenced if the reaction system was properly designed. Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N-O bond to produce both an amino and a hydroxy functionality, allows the synthesis of many products of potential interest.

Over the years, nitrones have become important building blocks in organic synthesis However, in spite of their well-documented utility there are only scattered reports
dealing with the preparation of nitrones with a chiral C-substituent.\(^5,6\) With the goal of developing a simple route to polyhydroxylated derivatives of pyrrolizidines, \(^7\) which have been shown to display antiviral activity, \(^8\) via an asymmetric 1,3-dipolar cycloaddition we have recently published the preparation of new D-erythrose- and D-threose-derived nitrones and the stereoselectivity of their cycloadditions to styrene.\(^9,10\)

In this paper we report the stereoselectivity of the cycloaddition of chiral sugar-derived nitrones \(1a,b\) and \(2a,b\) with \(N\)-phenylmaleimide (3) and the chiral maleimides 12 and 13.

**Results and Discussion**

The diastereomerically pure \((Z)\)-nitrones \(1a,b\) and \(2a,b\) were subjected to 1,3-dipolar cycloaddition reactions. Our task was to study the asymmetric induction from the nitrone part. There are four possible products; \(cis\)- and \(trans\)-isomers from \(anti\)- and \(syn\)-attack (Scheme 1). With each of the nitrones the reaction proceeded smoothly in high yields.

The structure assignments of the products are based on straightforward analysis of NMR spectra. The stereochemistry of the cycloadducts was deduced by their NOE experiments. The most important and decisive information obtained from these experiments is the presence or absence of the NOE interaction between the protons 3-H/3a-H and 6a-H/3-H in the corresponding \(exo\)- and \(endo\)-cycloadducts, respectively. Finally, the relative 3-C/4-C \(erythro\)-configuration in the isolated adducts was assigned by comparison with the analogue prepared by the cycloaddition from nitrone \(1a\) with styrene, the structure of which was elucidated by X-ray analysis.\(^10\) The ratio of diastereoisomers was determined from \(^13\)C NMR spectra by integration of the peaks of the 3a-C signals of the isoxazolidine products.
The cycloadditions were first carried out in boiling toluene with N-phenylmaleimide (3). In the case of D-erythro-derived nitrones 1a,b only two diastereoisomers, erythro-trans 4a,b and threo-trans 5a,b were formed (entries 1 and 2, Table 1). 3,3a-cis-Disubstituted endo-adducts 6 and 7 were not detected in the crude reaction mixture by NMR spectra (Scheme 1). The cycloadducts 4a,b and 5a were separated by column chromatography.

Table 1. 1,3-Dipolar cycloaddition of C-α-alkoxyalkyl-substituted nitrones to maleimides

| Entry | Imide | Nitrone | Yield (%) | erythro-trans | erythro-cis | threo-trans | threo-cis | erythro:trans:threo:trans-|cis |
|-------|-------|---------|-----------|---------------|-------------|-------------|-----------|-----------------------------|
| 1     | 3     | 1a      | 90        | 50            | –           | 50          | –         | 50:50                       | >95:5 |
| 2     | 3     | 1b      | 74        | 63            | –           | 37          | –         | 63:37                       | >95:5 |
| 3     | 3     | 1ba     | 66        | 39            | 6           | 55          | –         | 45:55                       | 94:6  |
| 4     | 3     | 2a      | 95        | 73            | 15          | 8           | 4         | 88:12                       | 81:19 |
| 5     | 3     | 2b      | 89        | 46            | 28          | 26          | –         | 74:26                       | 72:28 |
| 6     | 3     | 2ba     | 90        | 46            | 32          | 17          | 5         | 78:22                       | 63:37 |
| 7     | 12    | 1a      | 70        | 43            | 18          | 25          | 14        | 61:39                       | 68:32 |
| 8     | 13    | 1a      | 69        | 51            | 7           | 42          | –         | 58:42                       | 93:7  |
| 9     | 13    | 1b      | 80        | 64            | –           | 36          | –         | 64:36                       | >95:5 |
| 10    | 12    | 2a      | 64        | 50            | 20          | 17          | 13        | 70:30                       | 67:33 |

a Microwave.

The analysis of product configuration indicates that 4a,b and 5a,b arise from a cycloaddition which has occurred on the more sterically accessible face of the nitrone, via an exo-transition state with syn periplanar relationship of the N-phenyl and N-benzyl group. Dipolar cycloaddition of C-α-alkoxy-substituted nitrones have been shown to occur preferentially via transition states in which the developing carbon-carbon bond avoids steric interaction with the more bulky group.2,10,11 We consider that both isoxazolidines 4 and 5 result from a 100% exo-attack of the dipolarophile maleimide (3) on the (Z)-nitrone 1a,b, because the corresponding (E)-nitrones were not detected by 1H NMR. There was no thermal interconversion between the prepared adducts in refluxing toluene, thus indicating that the cycloaddition proceeded irreversibly under the reaction conditions to give the kinetically controlled products 4 and 5, respectively. Such total exo selectivity may be ascribed to the steric interaction in the transition state between the phenyl group of maleimide (3) and the heterocyclic moiety of the nitrone 1a,b in corresponding endo-transition state that would lead to the cycloadducts 6a,b and 7a,b.

The reaction of D-threo-derived nitrone 2a with 3 furnished the corresponding cycloadducts 8a, 9a, 10a and 11a in a ratio of 73:15:8:4 (Entry 4, Table 1). The minor product 10a was isolated as a pure compound. On the other hand, from the reaction of protected D-threo-derived nitrone 2b with 3 all three cycloadducts 8b, 9b and 10b were isolated in a pure state 46:28:26 (Entry 5, Table 1).
The diastereofacial selectivities of the above-mentioned cycloadditions are highly dependent on the structures of nitrone and maleimide. While the reactions employing D-erythro-derived nitrones 1a,b (Entries 1–3, Table 1) gave poor anti-selectivities, the reactions using D-threo-derived nitrones 2a,b gave good stereoselectivities (entries 4-6, Table 1). The lowest erythro:threo ratio of 50:50 has been observed in the case of D-erythro-derived nitrone 1a (Entry 1, Table 1). These differences in anti/syn-selectivity can be rationalized by considering the transition states in the cycloaddition (Figure 1). Since the cycloadditions proceed from (Z)-nitrone preferentially via the less hindered exo-transition state and in an antiperiplanar manner with respect to the largest group of the heterocyclic acetal, the methyl substituent in the nitrone is oriented in the syn/anti-position relative to the maleimide 3. Accordingly, the use of D-threo-derived nitrones 2a and 2b having the methyl group in the axial position gave better selectivities. The diastereofacial selectivities observed are comparable to the previously published results obtained by the cycloadditions of these nitrones with styrene10 as well as to results reported for a cyclic nitrone with N-benzylmaleimide.12

Next, the nitrones 1a,b and 2a were treated with chiral maleimides 12 and 13 (Schemes 2 and 3). The exo-product, erythro-trans 14, 18, and 22 was isolated as the major isomer in each case. The diastereofacial selectivities of the cycloaddition to chiral maleimides 12 and 13 are only moderate (Entries 7-10, Table 1). Although the chiral maleimides 12 and 13 are enantiomers, the product ratios of formed isoxazolidines resulting from the cycloaddition of the D-erythro-derived nitrone 1a are not similar. The stereogenic centre in chiral maleimides has an influence on the trans:cis ratio of the isomers formed (68:32 and 93:7, Entries 7 and 8, Table 1). On the other hand, in the reaction of the protected D-erythro derived nitrone 1b with the chiral maleimide 13 only two exo-diastereoisomers, erythro-trans 18b and threo-trans 19b were formed (Entry 9, Table 1).
It is noteworthy that our attempts to accelerate the cycloaddition by microwave irradiation were successful. Indeed, microwave irradiation dramatically decreased the reaction times of the cycloadditions. For example, in the case of the cycloaddition of nitronate 1b with dipolarophile 3, the reaction time decreased from 11 h to 8 min. Moreover, microwave irradiation could even reverse the ratio of erythro-trans / erythro-cis adducts from 63:37 to 39:55 for 1b (Entries 2 and 3, Table 1). To the best of our knowledge this reversal of stereoselectivity of the nitronate cycloaddition using microwave irradiation is a very rare phenomenon. On the other hand, in the case of the cycloaddition of nitronate 2b to imide 3 microwave irradiation only slightly changed the ratio of diastereomers (Entry 6, Table 1) while the reaction time decreased from 3 h to 10 min.

Experimental Section

General Procedures. All starting materials and reagents are commercially available (Fluka, Merck or Avocado) and were used without further purification. Solvents were dried before use.
Thin-layer chromatography (TLC, on aluminium plates coated with silica 60F254, 0.25 mm thickness, Merck) was used for monitoring of reaction courses; eluents are given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040–0.063 mm, Merck). Melting points (mp) were determined on a Kofler hot plate apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Department of Analytical Chemistry, Slovak University of Technology, Bratislava.

The 1H and 13C NMR spectra of deuterochloroform solutions were obtained using Varian VXR 300 (300 MHz) and Bruker DRX-400 (400 MHz) instruments, tetramethylsilane being the internal reference. Optical rotations [α] were measured on an IBZ Messtechnik Polar-LµP polarimeter at the sodium D line (589 nm) using a 1 dm cell with chloroform as solvent. The nitrones 1a,b and 2a,b were prepared from the corresponding aldehydes by the reaction with N-benzylhydroxylamine in dichloromethane in the presence of anhydrous magnesium sulfate according to the procedure used in the literature for the preparation of chiral N-benzyl nitrones. Previously described methods were used to prepare the corresponding aldehydes and maleimides.

(3S,3aR,6aS)-2-benzyl-3-[(2S,4R,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-phenylperhydropyrrolo[3,4-d]isoxazole-4,6-dione (4a) and (3R,3aR,6aR)-2-benzyl-3-[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-phenylperhydropyrrolo[3,4-d]isoxazole-4,6-dione (5a). To a stirred solution of the nitrone 1a (378 mg, 1.5 mmol) in toluene (10 mL) was added N-phenylmaleimide (300 mg, 1.73 mmol), and the solution was heated at reflux for 10 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of two diastereoisomers 4a and 5a (ratio 50:50 by 13C NMR) was purified and separated by column chromatography on silica gel (2.5 x 32 cm) eluting with EtOAc/isohexane (33:67) to give 4a as a first fraction (303.4 mg, 45%) and 5a as the second fraction (303.6 mg, 45%); combined yield 607 mg (90%).

**4a.** Colourless crystals, Rf = 0.25 (EtOAc/isohexane 33:67); mp 185–186 °C; [α] = +50.7 (c 1.2, CHCl3). 1H NMR (400 MHz, CDCl3/TMS): δ 7.54–7.23 (m, 10H, H Ph), 5.10 (d, 1H, J = 8.0 Hz, H-6a), 4.66 (q, 1H, J = 5.0 Hz, 2-H), 4.33 (d, 1H, J = 12.0 Hz, CHAxBPh), 4.29 (br s, 1H, OH), 4.22 (dd, 1H, J = 1.5, 8.0 Hz, 3a-H), 4.08 (dd, 1H, J = 4.0, 10.1 Hz, 6A-H), 4.01 (dd, 1H, J = 1.5, 8.3 Hz, 3-H), 3.81 (d, 1H, J = 12.0 Hz, CHAxBPh), 3.39–3.25 (m, 3H, 4-H, 5-H, 6 B-H), 1.36 (d, 3H, J = 5.0 Hz, CH3). 13C NMR (100.6 MHz, CDCl3/TMS): δ 175.3, 173.5 (2 C=O), 134.3, 131.7 (2C, 1-CPh), 129.9, 129.6, 129.5, 129.3, 129.2, 126.1, (10C, 2-6CPh), 99.7 (2-C), 78.6 (6a-C), 77.9 (4-C), 70.6 (3-C), 70.2 (6-C), 65.9 (4-C), 63.6 (CH2Ph), 51.8 (3a-C), 20.9 (2-CH3). Anal. calcd. for C23H24N2O6 (424.45): C, 65.08, H, 5.70, N, 6.60. Found: C, 64.81, H, 5.73, N, 6.52.

**5a.** Colourless crystals, Rf = 0.18 (EtOAc/isohexane 33:67); mp 193–194 °C; [α] = –33.6 (c 1.1, CHCl3). 1H NMR (400 MHz, CDCl3/TMS): δ 7.55–7.26 (m, 10 H, HPh), 4.98 (d, 1H, J = 7.7 Hz, 6a-H), 4.65 (q, 1H, J = 5.0 Hz, 2-H), 4.28 (d, 1H, J = 12.6 Hz, CHAxBPh), 4.14 (dd, 1H, J = 3.2, 7.7 Hz, 3a-H), 4.08 (dd, 1H, J = 5.4, 10.0 Hz, 6A-H), 4.04 (d, 1H, J = 12.6 Hz, CHAxBPh), 3.88
(dd, 1H, J = 3.2, 5.5 Hz, 3-H), 3.69 (m, 1H, 5-H), 3.60 (dd, 1H, J = 5.5, 9.0 Hz, 4-H), 2.77 (br, 1H, OH), 1.33 (d, 3H, J = 5.0 Hz, CH3). 13C NMR (100.6 MHz, CDCl3/TMS): δ 176.5, 172.6 (2 C=O), 135.9, 130.1 (2C, 1-CPh), 130.1, 129.6, 129.3, 129.2, 128.7, 126.4, (10C, 2-6CPh), 99.4 (2-C), 82.0 (3-C), 78.5 (6a-C), 70.2 (6-C), 67.8 (3-C), 63.8 (CH2Ph), 63.2 (4-C), 52.2 (3a-C), 20.8 (2-CH3). Anal. calcd. for C23H24N2O6, (424.45): C, 65.08, H, 5.70, N, 6.60. Found: C, 64.90, H, 5.60, N, 6.69.

(3S,3aR,6aS)-2-Benzyl-3-[(2S,4R,5R)-5-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methyl-1,3-dioxan-4-yl]-5-phenylderhydropyrrole[3,4-d]isoxazole-4,6-dione (4b). To a stirred solution of the nitrone 1b (50 mg, 0.14 mmol) in toluene (2.5 mL) was added N-phenylmaleimide (30 mg, 0.16 mmol), and the reaction was heated at reflux for 11 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of two diastereoisomers 4b and 5b (73 mg, 99%; ratio 63:37; 13C NMR) was purified by column chromatography on silica gel (1.0 x 23 cm) eluting with EtOAc/isohexane (40:60) to give pure 4b and an unseparable mixture of diastereoisomers 4b and 5b.

4b. Colourless crystals, Rf = 0.64 (EtOAc/isohexane 50:50), Rf = 0.40 (EtOAc/isohexane 30:70); mp 119-120 °C. 1H NMR (300MHz, CDCl3/TMS): δ 7.56–7.26 (m, 10H, H Ph), 4.99 (d, 1H, J = 7.6 Hz, 6a-H), 4.77 (q, 1H, J = 5.0 Hz, 2-H), 4.28 (d, 1H, J = 13.2 Hz, CHAaPh), 4.15 (dd, 1H, J = 7.6, 2.6 Hz, 3a-H), 4.07 (dd, 1H, J = 10.8, 9.6 Hz, 6a-H), 3.99 (dd, 1H, J = 2.6, 2.6 Hz, 3-H), 3.98 (d, 1H, J = 13.2 Hz, CHAaPh), 3.69–3.65 (m, 2H, 4-H, 5-H), 3.38 (dd, 1H, J = 10.8 Hz, 6b-H), 1.34 (d, 3H, J = 5.0 Hz, CH3), 0.77 [s, 9H, C(CH3)3], 0.08, 0.07 [2s, 3H, 3H, Si(CH3)2]. 13C NMR (75 MHz, CDCl3/TMS): δ 175.6, 173.2 (2 C=O), 135.5, 131.5 (2C, 1-CPh), 129.9, 128.6, 127.9, 126.0 (10C, 2-6CPh), 98.5 (2-C), 82.9 (4-C), 78.4 (6a-C), 71.9 (6-C), 66.5 (3-C), 63.5 (CH Ph), 62.9 (5-C), 50.3 (3a-C), 25.6 [C(CH3)3], 20.4 (2-CH3), 17.7 [C(CH3)3], –4.3 and –4.9 [2C, Si(CH3)2].

Microwave irradiation. To a stirred solution of the nitrone 1b (300 mg, 0.82 mmol) in toluene (15 mL) was added N-phenylmaleimide (3) (170 mg, 0.92 mmol) and the reaction was heated at reflux for 7.5 min. The resulting mixture was evaporated under reduced pressure. The crude mixture of three diastereoisomers 4b, 5b and 6b (ratio 39:6:55; 13C NMR) was purified by column chromatography on silica gel (2.0 x 28 cm) eluting with EtOAc/isohexane (40:60) to give a mixture of three diastereoisomers (290 mg, 66%).

(3R,3aS,6aR)-2-Benzyl-3-[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-phenylderhydropyrrole[3,4-d]isoxazole-4,6-dione (8a) and (3S,3aR,6aS)-2-Benzyl-3-[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-phenylderhydropyrrole[3,4-d]isoxazole-4,6-dione (10a). To a stirred solution of the nitrone 2a (500 mg, 2.0 mmol) in toluene (10 mL) was added N-phenylmaleimide (3) (517 mg, 3.0 mmol) and the reaction was heated at reflux for 4 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of four diastereoisomers 8a, 9a, 10a and 11a (ratio 73:15:8:≤4; 13C NMR) was purified and separated by column chromatography on silica gel (2.5 x 32 cm) eluting with EtOAc/isohexane (54:46) to give product 10a as a first fraction (60 mg, 7%) and a mixture of diastereomers 8a, 9a
and 11a (680 mg, 81%); combined yield 740 mg (89%).

10a. Colourless solid, mp = 103–105 °C. 1H NMR (400 MHz, CDCl₃/TMS): δ 7.57–7.19 (m, 10H, HPh), 4.76 (m, 2H, 5-H, 2-H), 4.33 (d, 1H, J = 8.0 Hz, 3a-H), 4.29 (d, 1H, J = 12.0 Hz, CH₃H₃Ph), 4.22–4.19 (m, 2H, 3-H, 6a-H), 3.79 (d, 1H, J = 12.9 Hz, H-6b-H), 3.71 (d, 1H, J = 12.0 Hz, CH₃H₃Ph), 3.60 (d, 1H, J = 9.6 Hz, 4-H), 1.41 (d, 3H, J = 5.0 Hz, CH₃). 13C NMR (100.6 MHz, CDCl₃/TMS): δ 175.4, 174.1 (2 C=O), 134.9, 131.8 (2C, 1-CPh), 129.9, 129.6, 129.5, 129.4, 128.7, 126.1, 125.7 (10C, 2-6C Ph), 100.1 (2-C), 78.8 (6a-C), 75.8 (4-C), 68.6 (6-C), 66.0 (3-C), 65.1 (5-C), 63.6 (CH₂Ph), 50.9 (3a-C), 21.1 (2-CH₃).

8a. 1H NMR (400 MHz, CDCl₃/TMS): δ 7.57–7.28 (m, 10H, HPh), 5.01 (d, 1H, J = 7.6 Hz, 6a-H), 4.75 (q, 1H, J = 5.0 Hz, 2-H), 4.25 (m, 2H, 3-H, 3a-H), 4.29 (d, 1H, J = 12.6 Hz, CH₂H₂Ph), 4.07 (dd, 1H, J = 12.0, 2.0 Hz, 6a-H), 3.90 (d, 1H, J = 12.5 Hz, CH₂H₂Ph), 3.79 (d, 1H, J = 12.0, 1.3 Hz, 6b-H), 3.69 (br s, 1H, 5-H), 3.49 (dd, J = 1.1, 9.3 Hz, 4-H), 1.41 (d, 3H, J = 5.0 Hz, CH₃). 13C NMR (100.6 MHz, CDCl₃/TMS): δ 175.5, 173.7 (2 C=O), 135.4, 131.8 (2C, 1-C Ph), 129.5, 129.4, 129.0, 128.6, 128.1, 126.3, 125.7 (10C, 2-6CPh), 99.9 (2-C), 78.2 (6a-C), 77.3 (4-C), 71.7 (6-C), 67.2 (3-C), 63.3 (CH₂Ph), 62.8 (5-C), 50.3 (3a-C), 20.8 (2-CH₃).

(3S,3aS,6aR)-2-Benzyl-3-[2(R,4S,5R)]-5-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methyl-1,3-dioxan-4-yl]-5-phenylperhydropyrrolo[3,4-d]isoxazole-4,6-dione (8b) and (3R,3aR,6aS)-2-Benzyl-3-[2(R,4S,5R)]-5-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methyl-1,3-dioxan-4-yl]-5-phenylperhydropyrrolo[3,4-d]isoxazole-4,6-dione (9b) and (3S,3aR,6aS)-2-Benzyl-3-[2(R,4S,5R)]-5-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methyl-1,3-dioxan-4-yl]-5-phenylperhydropyrrolo[3,4-d]isoxazole-4,6-dione (10b). To a stirred solution of the nitrone 2b (539 mg, 1.5 mmol) in toluene (25 mL) was added N-phenylmaleimide (3) (255 mg, 1.5 mmol), and the reaction was heated at reflux for 3 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of three diastereoisomers (ratio 46:28:26 by 13C NMR) was purified by column chromatography on silica (3.0 x 24 cm) eluting with EtOAc/isohexane (90:10 → 50:50) to give as first fraction the minor diastereoisomer 9b (109 mg, 14%), as second fraction the major product 8b (279 mg, 35%), and as the third fraction the minor product 10b (203 mg, 26%); combined yield 591 mg (75%).

Major product 8b. Colourless oil, Rf = 0.42 (EtOAc/isohexane 60:40); [α] = +22.4 (c = 0.3, CHCl₃). 1H NMR (300 MHz, CDCl₃/TMS): δ 7.54–7.25 (m, 10H, HPh), 4.92 (d, 1H, J = 8.0 Hz, 6a-H), 4.74 (q, 1H, J = 5.0 Hz, 2-H), 4.38 (dd, 1H, J = 8.0 Hz, 3a-H), 4.26 (dd, 1H, J = 8.3, 0.8 Hz, 3-H), 4.10–3.99 (m, 2H, J = 13.9, 12.5, 0.6 Hz, 6a-H, CH₂H₃Ph), 3.88 (d, 1H, J = 13.9 Hz, CH₂H₃Ph), 3.85 (br, 1H, J = 1.5, 1.5, 0.6 Hz, 5-H), 3.73 (dd, 1H, J = 12.5, 1.5 Hz, 6b-H), 3.50 (dd, 1H, J = 8.3, 1.5 Hz, 4-H), 1.38 (d, 3H, J = 5.0 Hz, CH₃), 0.93 [s, 9H, C(CH₃)₃], 0.15, 0.09 [2s, 3H, 3H, Si(CH₃)₂]. 13C NMR (75 MHz, CDCl₃/TMS): δ 175.7, 173.9 (2 C=O), 136.1, 131.5 (2C, 1-CPh), 129.4, 128.8, 128.5, 127.8, 125.9, 125.7 (10C, 2-6CPh), 99.2 (2-C), 78.0 (6a-C), 77.9 (4-C), 71.1 (6-C), 68.4 (3-C), 64.4 (5-C), 62.9 (CH₂Ph), 50.6 (3a-C), 25.9 [C(CH₃)₃], 20.9 (2-CH₃), 18.2 [C(CH₃)₃], −4.0, −4.2 [2C, Si(CH₃)₂].

9b. Colourless oil, Rf = 0.51 (EtOAc/isohexane 60:40); [α] = −45.4 (c = 0.3, CHCl₃). 1H NMR (300 MHz, CDCl₃/TMS): δ 7.53–7.24 (m, 10H, HPh), 4.85 (d, 1H, J = 7.5 Hz, 6a-H), 4.72 (d, 1H,
$J = 15.4 \text{ Hz, } \text{CHA}$\text{HPh}$), 4.71 (q, 1H, \text{J} = 5.1 \text{ Hz, 2-H}), 4.45 (br, 1H, \text{J} = 1.6, 1.6 Hz, 6a-H, 6b-H), 3.94 (dd, 1H, \text{J} = 9.6, 1.6 Hz, H-4), 3.64 (dd, 1H, \text{J} = 7.2, 7.5 Hz, H-3a), 3.51 (dd, 1H, \text{J} = 7.2, 9.6 Hz, 3-H), 1.34 (d, 3H, \text{J} = 5.1 Hz, CH$_3$), 0.95 [s, 9H, C(CH$_3$)$_3$], 0.19, 0.12 [2s, 3H, 3H, Si(CH$_3$)$_2$].

$^{13}$C NMR (75 MHz, CDCl$_3$/TMS): $\delta$ 173.5, 173.4 (2 C=O), 136.3, 131.3 (2C, 1-C Ph), 129.2, 129.1, 128.9, 128.0, 126.9, 126.3 (10C, 2-6C Ph), 98.6 (2-C), 78.1 (4-C), 74.7 (6a-C), 71.0 (6-C), 66.3 (3-C), 64.6 (5-C), 60.3 (C$_2$H$_2$Ph), 49.4 (3a-C), 25.9 [C(CH$_3$)$_3$], 20.9 (2-CH$_3$), 18.3 [SiC(CH$_3$)$_3$], –3.7 and –4.3 [2C, Si(CH$_3$)$_2$].

**10b.** Colourless oil, $R_f = 0.22$ (EtOAc/isohexane 60:40); $[\alpha] = –21.2$ (c = 0.3, CHCl$_3$). $^1$H NMR (300 MHz, CDCl$_3$/TMS): $\delta$ 7.51–7.25 (m, 10H, HPh), 4.85 (d, 1H, \text{J} = 7.6 Hz, 6a-H), 4.80 (q, 1H, \text{J} = 5.0 Hz, 2-H), 4.24, 4.15 (2d, 1H, 1H, \text{J} = 14.1 Hz, C$_2$H$_2$Ph), 4.12 (dd, 1H, \text{J} = 12.5, 1.7 Hz, 6A-H), 3.94 (dd, 1H, \text{J} = 8.7, 3.0 Hz, 3-H), 3.82–3.75 (m, 2H, 4-H, 5-H), 3.77 (dd, 1H, \text{J} = 12.5, 1.4 Hz, 6B-H), 3.67 (dd, 1H, \text{J} = 7.6, 3.0 Hz, 3a-H), 1.38 (d, 3H, \text{J} = 5.0 Hz, CH$_3$), 0.93 [s, 9H, C(CH$_3$)$_3$], 0.15, 0.13 [2s, 3H, 3H, Si(CH$_3$)$_2$]. $^{13}$C NMR (75 MHz,): $\delta$ 173.89, 172.68 (2 C=O), 136.5, 131.4 (2C, 1-C Ph), 129.3, 128.9, 128.3, 127.4, 126.2, (10C, 2-6C Ph), 98.9 (2-C), 78.3 (4-C), 76.4 (6a-C), 71.2 (6-C), 67.2 (3-C), 64.8 (5-C), 60.4 (CH$_2$Ph), 51.1 (3a-C), 25.9 [C(CH$_3$)$_3$], 20.9 (2-CH$_3$), 18.4 [C(CH$_3$)$_3$], –3.8 and –4.1 [2C, Si(CH$_3$)$_2$].

Microwave irradiation. To a stirred solution of the nitrone 2b (100 mg, 0.27 mmol) in toluene (5 mL) was added N-phenylmaleimide (3) (47 mg, 0.27 mmol) and the reaction was carried out under microwave irradiation (1000 W) in toluene for 10 min as before. The resulting mixture was evaporated under reduced pressure. The crude mixture of three diastereoisomers 8b, 9b, 10b (ratio 46:5:32:17 by $^{13}$C NMR) was purified by column chromatography on silica gel (2.0 x 16 cm) eluting with EtOAc/isohexane (30:70) to give a mixture of three diastereoisomers (133 mg, 90%).

$^{(3R,3aS,6aR)}$-2-benzyl-3-[(2S,4R,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-[(1R)-(1-phenylethyl)]perhydropyrrolo[3,4-d]isoxazole-4,6-dione (15) and $^{(3S,3aR, 6aS)}$-2-benzyl-3-[(2S,4R,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-[(1R)-(1-phenyl-ethyl)]-perhydropyrrolo[3,4-d]isoxazole-4,6-dione (14). To a stirred solution of the nitrone 1a (250 mg, 1.0 mmol) in toluene (10 mL) was added N-(1-phenylethyl)maleimide (12) (200 mg, 1.0 mmol), and the reaction was heated at reflux for 10 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of four diastereoisomers (ratio 43:18:25:14 by $^{13}$C NMR) was purified by column chromatography on silica gel (2.0 x 20 cm) eluting with EtOAc/petroleum ether (40:60) to give mixture of all diastereoisomers (315 mg, 70%). The mixture of diastereoisomers was separated by column chromatography on silica gel (2.0 x 35 cm, EtOAc/petroleum ether 25:75) affording only the major product 14 and one minor product 15.

**14.** Colorless solid, $R_f = 0.53$ (EtOAc/petroleum ether 50:50); mp = 57–59 °C. $^1$H NMR (400 MHz, CDCl$_3$/TMS): $\delta$ 7.56–7.53 (m, 2H, HPh), 7.38–7.28 (m, 6H, HPh), 7.00-6.96 (m, 2H, HPh), 5.48 (q, 1H, J = 7.3 Hz, CH$_3$CHPh), 4.82 (d, 1H, J = 7.8 Hz, 6a-H), 4.59 (q, 1H, J = 5.0 Hz, 2-H), 4.59 (dd, 1H, J = 5.4, 10.8 Hz, 6a-H), 4.00 (d, 1H, J = 12.3 Hz, CH$_2$H$_2$Ph), 3.90 (dd, 1H, J = 2.7, 7.9 Hz, 3a-H), 3.64 (dd, 1H, J = 2.6, 5.0 Hz, 3-H), 3.58 (m, 1H, 5-H), 3.40 (dd, 1H, J = 5.3,
9.1 Hz, 4-H), 3.35 (d, 1H, J = 12.3 Hz, CH₃H₃Ph), 3.34 (dd, 1H, J = 10.8, 10.5 Hz, 6a-H), 2.64 (br s, 1H, OH), 1.90 (d, 3H, J = 7.3 Hz, CH₂CH₃Ph), 1.31 (d, 3H, J = 5.0 Hz, CH₃). ¹³C NMR (100.6 MHz, CDCl₃/TMS): δ 176.9, 173.9 (2 C=O), 138.1, 135.7 (2C, 1-CPh), 129.9, 129.7, 129.3, 129.1, 129.0, 128.9, 128.8, 128.5, 128.5 (10C, 2-6CPh), 99.4 (2-C), 81.6 (4-C), 78.7 (6a-C), 70.1 (6-C), 67.2 (3-C), 63.2 (CH₂Ph), 62.9 (5-C), 51.5 (2C, 5-CH₃CHPh, 3a-C), 20.9 (2-CH₃), 16.3 (5-CH₃CHPh).

15. Colorless solid, Rₓ = 0.53 (EtOAc/petroleum ether 50:50); mp = 75–78 ºC. ¹H NMR (400 MHz, CDCl₃/TMS): δ 7.67–7.58 (m, 2H, HPh), 7.27–7.16 (m, 6H, HPh), 6.85–6.83 (m, 2H, HPh), 5.41 (q, 1H, J = 7.3 Hz, CH₃CHPh), 4.79 (d, 1H, J = 7.9 Hz, 6a-H), 4.52 (q, 1H, J = 5.0 Hz, 2-H), 4.39 (br s, 1H, OH), 4.95 (dd, 1H, J = 4.7, 10.8 Hz, 6a-H), 3.86 (dd, 1H, J = 1.2, 8.2 Hz, 3a-H), 3.68 (d, 1H, J = 11.9 Hz, CH₃H₃Ph), 3.68 (m, 1H, 3-H), 3.29 (dd, 1H, J = 10.8, 9.6 Hz, 6b-H), 3.20–3.11 (m, 2H, 4-H, 5-H), 3.17 (d, 1H, J = 11.9 Hz, CH₃H₃Ph), 1.90 (d, 3H, J = 7.3 Hz, CH₃CHPh), 1.20 (d, 3H, J = 5.0 Hz, CH₃). ¹³C NMR (100.6 MHz, CDCl₃/TMS), δ 175.7, 174.5 (2 C=O), 138.0, 134.3 (2C, 1-CPh), 129.8, 129.3, 129.1, 129.0, 128.8, 128.5, 127.9, 126.8, 126.3, 126.2 (10C, 2-6CPh), 99.6 (2-C), 78.4 (4-C), 78.0 (6a-C), 70.4 (3-C), 70.0 (6-C), 65.8 (5-C), 63.2 (CH₂Ph), 52.2 (5-CH₃CHPh), 51.6 (3a-C), 20.9 (2-CH₃), 16.3 (5-CH₃CHPh).

(3R,3aS,6aR)-2-benzyl-3-[(2S,4R,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-[(15S)-1-phenylethyl]perhydropyrrolo[3,4-d]isoxazole-4,6-dione (19a) and (3S,3aR,6aS)-2-benzyl-3-[(2S,4R,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-[(15S)-1-phenylethyl]perhydropyrrolo[3,4-d]isoxazole-4,6-dione (18a). To a stirred solution of the nitrone 1a (312, 1.24 mmol) in toluene (15 mL) was added N-(1-phenylethyl)maleimide (13) (250 mg, 1.24 mmol), and the reaction was heated at reflux for 10 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of three diastereoisomers (ratio 51:7:42 by ¹³C NMR) was purified and separated by column chromatography on silica gel (2.0 x 35 cm eluting with EtOAc/petroleum ether (25:75) to give first mixture of all diastereoisomers (111 mg, 20%) and cycloadducts 18a and 19a (279 mg, 49%) as second fraction.

19a. Rₓ = 0.52 (EtOAc/petroleum ether 50:50). ¹H NMR (300 MHz, CDCl₃/TMS): δ 7.57–7.55 (m, 2H, HPh), 7.33–7.20 (m, 6H, HPh), 6.79–6.76 (m, 2H, HPh), 5.49 (q, 1H, J = 7.4 Hz, CH₃CHPh), 4.90 (d, 1H, J = 8.1 Hz, 6a-H), 4.56 (q, 1H, J = 5.0 Hz, CH₃), 4.37 (br, 1H, OH), 3.97 (dd, 1H, J = 4.9, 10.9 Hz, 6a-H), 3.89 (dd, 1H, J = 1.2, 8.1 Hz, 3a-H), 3.86 (d, 1H, J = 12.0 Hz, CH₃H₃Ph), 3.63 (dd, 1H, J = 1.2, 7.0 Hz, 3-H), 3.25 (dd, 1H, J = 9.6, 11.0 Hz, 6b-H), 3.08 (m, 2H, 4-H, 5-H), 2.99 (d, 1H, J = 12.0 Hz, CH₃H₃Ph), 2.64 (br s, 1H, OH), 1.90 (d, 3H, J = 7.4 Hz, CH₃CHPh), 1.26 (d, 3H, J = 5.0 Hz, CH₃). ¹³C NMR (75 MHz, CDCl₃/TMS): δ 175.7, 174.5 (2 C=O), 137.6, 134.1 (2C, 1-CPh), 129.8, 129.2, 129.0, 128.9, 128.7, 127.8 (10C, 2-6CPh), 99.6 (2-C), 78.5 (6a-C), 78.0 (4-C), 70.0 (6-C, 3-C), 65.7 (5-C), 63.3 (CH₂Ph), 51.8 (5-CH₃CHPh), 51.6 (3a-C), 20.9 (2-CH₃), 16.0 (5-CH₃CHPh).

18a. Rₓ = 0.52 (EtOAc/petroleum ether 50:50). ¹H NMR (400 MHz, CDCl₃/TMS): δ 7.57–7.50 (m, 2H, HPh), 7.32–7.26 (m, 6H, HPh), 7.05–7.02 (m, 2H, HPh), 5.48 (q, 1H, J = 7.4 Hz, CH₃CHPh), 4.79 (d, 1H, J = 7.9 Hz, 6a-H), 4.58 (q, 1H, J = 5.0 Hz, CH₃), 4.04 (dd, 1H, J = 5.4, 10.8 Hz, 6a-H), 3.90 (d, 1H, J = 12.7 Hz, CH₃H₃Ph), 3.90 (dd, 1H, J = 2.8, 7.9 Hz, 3a-H), 3.70
(dd, 1H, J = 2.8, 5.3 Hz, 3-H), 3.58 (m, 1H, 5-H), 3.35 (d, 1H, J = 12.6 Hz, CHA\(H_b\)Ph), 3.42 (dd, 1H, J = 5.3, 9.1 Hz, 4-H), 3.30 (dd, 1H, J = 10.8, 10.1 Hz, 6a-H), 2.77 (br s, 1H, OH), 1.87 (d, 3H, J = 5.0 Hz, CH\(_3\)). \(^{13}\)C NMR (100.6 MHz, CDCl\(_3/\)TMS): \(\delta\) 176.9, 174.0 (2 C=O), 138.5, 135.8 (2C, 1-C Ph), 129.9, 129.8, 129.3, 129.1, 129.0, 128.8, 128.4, 128.3 (10C, 2-6C Ph), 99.3 (2-C), 81.6 (4-C), 78.5 (6a-C), 70.1 (6-C), 67.7 (3-C), 63.4 (CH\(_2\)Ph), 62.9 (5-C), 51.9 (5-CH\(_3\)CHPh), 51.5 (3a-C), 20.8 (2-CH\(_3\)Ph), 16.5 (5-CH\(_3\)CHPh).

\(3S,3aR,6aS\)-2-benzyl-3-[(2S,4R,5R)-5-[(1S)-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methyl-1,3-dioxan-4-yl]-5-[(1S)-1-phenylethyl]perhydropyrrolo[3,4-d]isoxazole-4,6-dione (18b). To a stirred solution of the nitrone 1b (260 mg, 0.71 mmol) in toluene (10 mL) was added (1S)-N\-(1-phenylethyl)maleimide (13) (180 mg, 0.89 mmol) and the reaction mixture was heated at reflux for 10 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of two diastereoisomers 18b and 19b (ratio 64:36 by \(^{13}\)C NMR) was purified by column chromatography on silica gel (2.0 x 20 cm) eluting with EtOAc/isohexane (3:97 → 20:80) to give a mixture of diastereoisomers (321 mg, 80%).

18b. Colourless oil, \(R_f = 0.41\) (EtOAc/isohexane 30:70). \(^1\)H NMR (400 MHz, CDCl\(_3/\)TMS): \(\delta\) 7.57–6.90 (m, 10H, H Ph), 5.51 (q, 1H, J = 7.3 Hz, CH\(_3\)C\(_6\)H\(_5\)), 4.71 (d, 1H, J = 7.9 Hz, 6a-H), 4.64 (q, 1H, J = 5.0, 2-H), 4.14 - 4.04 (m, 3H, 3-H, 4-H, 6a-H), 3.86 (dd, 1H, J = 7.9, 2.1 Hz, 3a-H), 3.60 (d, 1H, J = 13.7 Hz, CHA\(H_b\)Ph), 3.52 (dd, 1H, J = 8.5, 3.5 Hz, 4-H), 3.41 (d, 1H, J = 13.7 Hz, CHA\(H_b\)Ph), 3.36 (dd, 1H, J = 9.9, 9.9 Hz, 6a-H), 1.90 (d, 3H, J = 7.6 Hz, CH\(_3\)CHPh), 1.30 (d, 3H, J = 5.0 Hz, CH\(_3\)), 0.88 [s, 9H, C(CH\(_3\))\(_3\)], 0.07, 0.06 [2s, 3H, 3H, Si(CH\(_3\))\(_2\)]. \(^{13}\)C NMR (75 MHz, CDCl\(_3/\)TMS): \(\delta\) 176.9, 174.8 (2 C=O), 138.4, 136.8 (2C, 1-C Ph), 129.1, 129.0, 128.7, 128.5, 128.4, 127.7 (10C, 2-6C Ph), 99.7 (2-C), 83.6 (4-C), 78.4 (6a-C), 71.6 (6-C), 68.1 (3-C), 63.7 (5-C, CH\(_2\)Ph), 52.7 (3a-C), 51.4 (5-CH\(_3\)CHPh), 26.2 [C(CH\(_3\))\(_3\)], 20.9 (2-CH\(_3\)H), 18.2 [C(CH\(_3\))]\(_2\), 16.3 (5-CH\(_3\)CHPh), -3.2, -4.1 [2C, Si(CH\(_3\))\(_2\)].

\(3S,3aR,6aS\)-2-benzyl-3-[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-[(1R)-1-phenylethyl]perhydropyrrolo[3,4-d]isoxazole-4,6-dione (22) and \(3R,3aR,6aS\)-2-Benzyl-3-[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]-5-[(1R)-1-phenyl-ethyl]phenylperhydropyrrolo[3,4-d]isoxazole-4,6-dione (23). To a stirred solution of the nitrone 2a (250 mg, 1.0 mmol) in toluene (10 mL) was added N\-(1-phenylethyl)-maleimide (12) (200 mg, 1.0 mmol) and the reaction mixture was heated at reflux for 10 h. The resulting mixture was evaporated under reduced pressure. The crude mixture of four diastereoisomers (ratio 50:20:17:13 by \(^{13}\)C NMR) was purified by column chromatography on silica gel (2.0 x 20 cm) eluting with EtOAc/petroleum ether (40:60) to give a mixture of all diastereoisomers 22–25 (288 mg, 64%). Separation of the mixture of diastereoisomers by column chromatography on silica gel (2.0 x 35 cm, EtOAc/petroleum ether, 25:75) afforded only the major product 22 and one minor product 23.

22. Colourless crystals, \(R_f = 0.28\) (EtOAc/ petroleum ether 50:50); mp 129–131 °C; [\(\alpha\)] = + 7.9 (c = 1.5, CHCl\(_3\)). \(^1\)H NMR (300 MHz, CDCl\(_3/\)TMS): \(\delta\) 7.57–7.54 (m, 2H, H\(_{\text{Ph}}\)), 7.34–7.20 (m, 6H, H\(_{\text{Ph}}\)), 6.92–6.87 (m, 2H, H\(_{\text{Ph}}\)), 5.46 (q, 1H, J = 7.5 Hz, CH\(_3\)CHPh), 4.76 (d, 1H, J = 8.1 Hz, 6a-H), 4.65 (q, 1H, J = 5.1 Hz, CH\(_3\)), 3.97 (dd, 1H, J = 1.2, 8.1 Hz, 3a-H), 3.94 (dd, 1H, J = 2.0, 9.9 Hz, 6a-H).
12.0 Hz, 6a-H), 3.88 (m, 1 H, J = 1.3, 2.0, 1.4, 9.6 Hz, 5-H), 3.69 (dd, 1H, J = 12.0, 1.4 Hz, 6a-H), 3.67 (d, 1H, J = 12.6 Hz, CHA\textsubscript{AB}Ph), 3.53 (m, 1H, 3-H), 3.33 (dd, 1H, J = 9.6, 1.3 Hz, 4-H), 3.22 (d, 1H, J = 12.6 Hz, CHA\textsubscript{AB}Ph), 2.16 (br s, 1H, OH), 1.87 (d, 3H, J = 7.5 Hz, CH\textsubscript{3}CHPh), 1.33 (d, 3H, J = 5.1 Hz, CH\textsubscript{3}). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}/TMS): \textsuperscript{δ} 176.6, 175.1 (2 C=O), 138.0, 135.9 (2C, 1-C\textsubscript{Ph}), 129.7, 129.1, 129.0, 128.9, 128.8, 128.6, 128.3 (10C, 2-6C\textsubscript{Ph}), 100.2 (2-C), 78.0 (6a-C), 77.9 (4-C), 72.1 (6-C), 67.0 (5-C), 63.3 (CH\textsubscript{2}Ph), 63.2 (3-C), 51.8 (5-CH\textsubscript{3}CHPh), 50.6 (3a-C), 21.3 (2-CH\textsubscript{3}), 16.2 (5-CH\textsubscript{3}CHPh).

23. Colourless oil \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}/TMS): \textsuperscript{δ} 7.47–7.44 (m, 2H, H\textsubscript{Ph}), 7.36–7.23 (m, 8H, H\textsubscript{Ph}), 5.48 (q, 1H, J = 7.3 Hz, CH\textsubscript{3}C\textsubscript{H}Ph), 4.63 (d, 1H, J = 7.3 Hz, 6a-H), 4.58 (d, 1H, J = 15.4 Hz, CHA\textsubscript{AB}Ph), 4.65 (q, 1H, J = 5.0 Hz, 2-H), 4.20 (m, 1H, 5-H), 3.95 (dd, 1H, J = 2.2, 12.0 Hz, 6a-H), 3.84 (d, 1H, J = 15.4 Hz, CHA\textsubscript{AB}Ph), 3.70 (dd, 1H, J = 12.0, 1.4 Hz, 6a-H), 3.56 (dd, 1H, J = 7.3, 7.0 Hz, 3a-H), 3.54 (dd, 1H, J = 9.6, 0.6 Hz, 4-H), 3.30 (dd, 1H, J = 9.6, 7.0 Hz, 3-H), 2.76 (br s, 1H, OH), 1.82 (d, 3H, J = 7.3 Hz, CH\textsubscript{3}CHPh), 1.27 (d, 3H, J = 5.0 Hz, CH\textsubscript{3}). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}/TMS): \textsuperscript{δ} 174.6, 174.5 (2 C=O), 139.4, 137.6 (2C, 1-C Ph), 128.7, 128.6, 128.5, 128.2, 127.8, 127.3 (10C, 2-6C\textsubscript{Ph}), 99.6 (2-C), 78.2 (4-C), 75.0 (6a-C), 72.1 (6-C), 67.3 (3-C), 64.3 (5-C), 60.8 (CH\textsubscript{2}Ph), 50.7 (5-CH\textsubscript{3}CHPh), 49.4 (3a-C), 21.2 (2-CH\textsubscript{3}), 16.5 (5-CH\textsubscript{3}CHPh).

Acknowledgements
The authors are grateful to the Slovak Grant Agency (No. 1/7314/20).

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