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Diels-Alder Reactions of Methyl *N*-*p*-methoxybenzensulfonylindole-2-(2-propenoate), a Convenient Dienophile Towards the Synthesis of Andranginine.

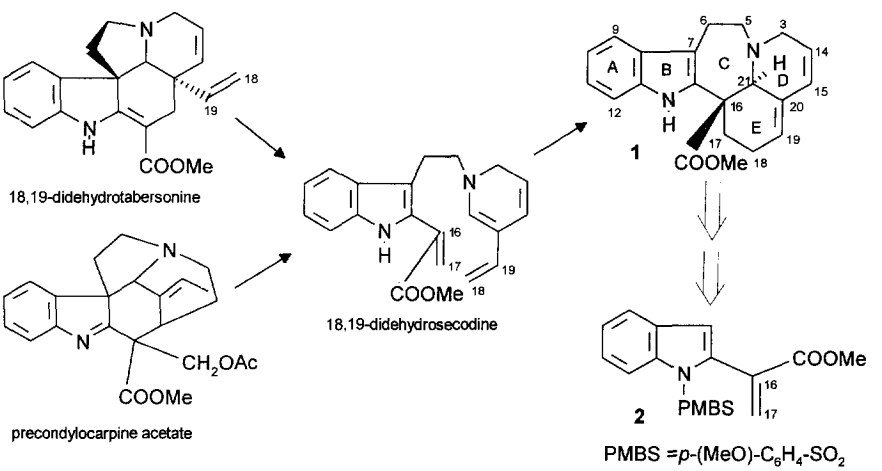
Bruno Danieli, Giordano Lesma, Marcello Luzzani, Daniele Passarella* and Alessandra Silvani

Dipartimento di Chimica Organica e Industriale - Università degli Studi di Milano -
Centro CNR di Studio sulle Sostanze Organiche Naturali -
Via Venezian 21 - 20133 Milano - Italia.

Abstract: Methyl *N*-*p*-methoxybenzensulfonylindole-2-(2-propenoate) (**2**) undergoes Diels-Alder reactions with silyloxybutadienes and 5-ethenylpyridinones to afford advanced intermediates for the total synthesis of (±)-andranginine (**1**).

INTRODUCTION

(±)-Andranginine **1** is a unique indole alkaloid possessing a perhydroazepine ring condensed to an hexahydroquinoline system, found in an Apocynaceae plant, *Craspidosperma verticillatum Boj. var. petiolare.*[1] Total synthesis of **1** has never been realized, but P. Potier *et al.* described semisynthesis by thermolysis of 18,19-didehydrotabersonine[1a] and precondylocarpine acetate[2] postulating an intramolecular [4 + 2]π cyclization of the 18,19-didehydrosecodine (Scheme).



Scheme

Pursuing our interest in the total synthesis of indole alkaloids we have examined the possibility of constructing the E ring of **1** with the proper functionalities by emulating the above cyclization in an intermolecular way *via* the reaction of a 2-vinylindole and a suitable substituted diene.

2-Vinylindoles have been widely used in the preparation of bioactive and pharmacological interesting compounds. In particular, the synthetic potential of 2-vinylindoles in cycloaddition has been explored mainly as 4π counterpart, as nicely shown in the synthesis of a great variety of carbazoles.[3,4]

The reactivity of the 2-vinylindole system is modulated according to the substituents present on the indole nitrogen and on the vinyl appendage. An electron withdrawing substituent on nitrogen has a beneficial effect on the reactivity of **2** as a dienophile[5] however only two studies related to this behaviour are reported in literature.[6]

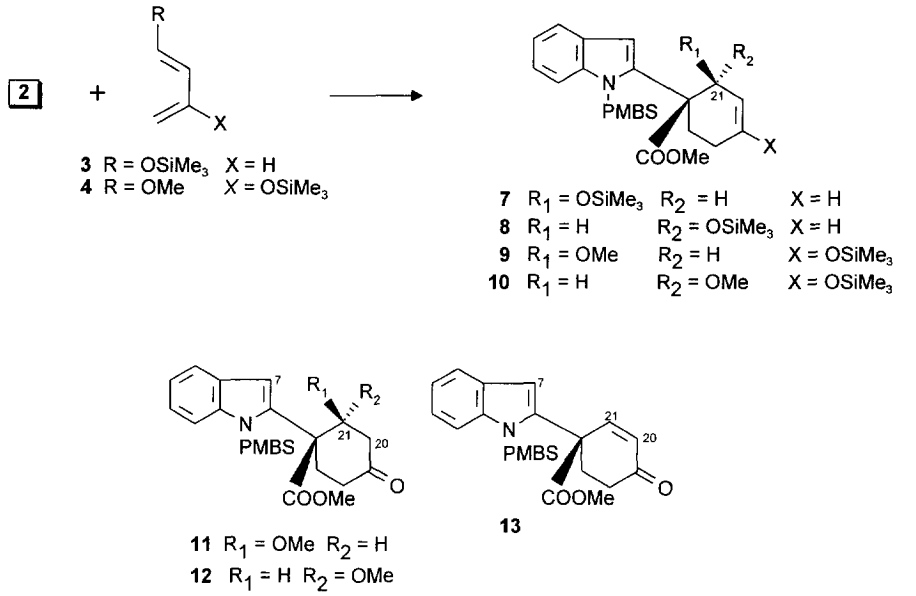
For the synthesis of **1** we devised the use of methyl *N*-*p*-methoxybenzensulfonilindole-2-(2-propenoate) **2**[7] and here we report the successful construction of ring E of **1** by reaction with the silyloxydienes **3** and **4** and with the more complex ethenyl dihydropyridinones **5** and **6**: the electron rich nature of these dienes combines for the success of the synthetic plan. Moreover, the cyclic dienes **5** and **6** furnish advanced intermediates for the total synthesis of **1** in which an additional ring is installed with a correct D/E ring junction.

RESULTS AND DISCUSSION

The indole acrylate **2** was prepared by reaction of 2-lithio-1-(*p*-MeO)-benzensulfonylindole with an excess of methyl pyruvate followed by acid-catalyzed dehydration according to the protocol described by Sundberg.[6a]

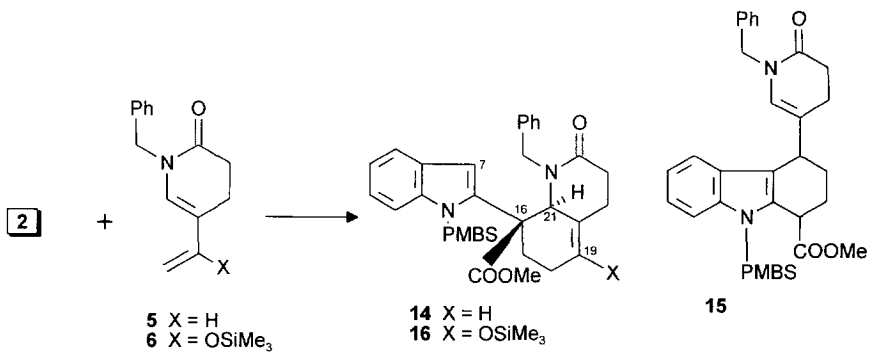
The reaction of **2** with trimethylsilyloxybutadiene **3** gave **7** and **8** deriving from the *exo* and the *endo* approaches of the reactants. The ^{1}H-NMR spectra of **7** and **8** were very similar and the two products could be distinguished by a NOE contact displayed by the signal at δ 6.60 (s, H-7) and 4.85 (d, H-21) of **7**. In the minimized structure[8] of **7** the distance between H-7 and H-21 was of 2.3 Å, consistent with a NOE interaction, while in the minimized structure of the epimer **8** the corresponding distance was 4.1 Å.

When 3-trimethylsilyloxymethoxybutadiene **4** was used as a diene the silyl enol ethers **9** and **10** were obtained. In the ^{1}H-NMR spectrum of compound **9** the signal of H-21 appeared as a doublet at δ 4.43 (J = 5.4 Hz), whereas it appeared as a broad singlet at δ 4.65 in the corresponding spectrum of compound **10**, resembling the characteristics of compounds **7** and **8**. A second similar feature was the signal of H-7 at δ 6.65 in compound **9** and at δ 7.04 in compound **10**, in accordance with the behaviour of H-7 in the ^{1}H-NMR spectrum of **7** and **8**. Hydrolysis of separated **9** and **10** with 5% H_3PO_4 gave the indolyl cyclohexanones **11** and **12** in which the H-21 signal appeared as a triplet respectively at δ 4.45 (**11**, J = 4 Hz) and at δ 4.52 (**12**, J = 4.5 Hz).



Treatment of compounds **9** and **10** with tetrabutylammonium fluoride easily afforded the indolylcyclohexenone **13** the ^{1}H-NMR spectrum of which contained two doublets (J = 9 Hz) at δ 7.28 (H-21) and 6.22 (H-20) for the α,β–unsaturated ketone moiety.

The regiochemical outcome of the cycloaddition reactions of **2** with **3** and **4,** in agreement with the predictions of the FMO concept,[9] prompted us to utilize ethenyldihydropyridinones **5**[10] and **6** as dienes, the aim being to simultaneusly introduce the E and D rings of the target skeleton.



In the reaction with **5,** compound **2** behaved like 2π and to a less extent like 4π-component to give a mixture of **14** and **15.** The relative configuration at C16 and C21 of compound **14**, the same as the natural

target, was ascertained by the presence of a NOE-effect between the signals at δ 4.61 (s, H-21) and 6.52 (s, H-7). The NOE interaction was detectable in the minimized structure of **14** but this is not the case in the minimized structure of the corresponding 16-epi-derivative. As regards the structure of **15**, it has been assigned on the basis of ^{1}H-NMR spectrum which showed the signals of benzylic protons next to carbomethoxy and dihydropyridinone groups at δ 4.33 (bt) and 3.55 (dd). ^{1}H-^{1}H-COSY experiment indicated that these signals are connected to different methylenic protons at δ 2.25 (1H), 1.93 (1H) and δ 1.85 (2H) respectively.

With the aim of improving the cyclization yield resulting in the hydroquinoline system, we thought to utilize the enol silyl ether **6**, obtained by reaction of the corresponding ketone[11] with LDA in THF and TMSCl at -78 ^{0}C. In fact refluxing **2** and **6** in toluene for 24 h, led to a derivative whose spectral data were in agreement with structure **16.**

The studies reported here demonstrate the utility of **2** for the construction of the E ring of the andranginine skeleton by [4+2]π cycloaddition. Moreover the use of 5-ethenyldihydropyridinones as dienes permits the diastereoselective attainment of derivatives containing E and D rings with the appropriate relative stereochemistry. The elaboration of **7-16** into the andranginine skeleton is presently in progress.

EXPERIMENTAL[10]

Methyl *N-p*-methoxybenzensulfonilindole-2-(2-propenoate) 2: *t*-BuLi (7.2 mmol) was added to a solution of *p*-methoxybenzensulfonilindole[12] (2 g, 6.97 mmol) in THF (50 ml) at -70 ^{0}C, and the mixture was stirred at -10 ^{0}C for 20 min. Then, methyl pyruvate (6.97 mmol) was added at -70 ^{0}C, and the temperature was allowed to reach room temperature. The mixture was poured into 5% NH_4Cl solution and extracted with Et_2O. The crude product obtained by concentration was directly dissolved in toluene (50 ml). *p*-TSA (100 mg) was added- and the solution was refluxed for 2 h. The reaction mixture was washed with 5% $NaHCO_3$ solution and evaporated to give after purification (Et_2O/Hexane 1:1) **2** (1.4 g, 55%). m.p. 136 ^{0}C; ^{1}H-NMR ($CDCl_3$) δ 8.10 (1H, d, J = 9 Hz), 7.63 (2H, AA` part of AA`BB`system), 7.45 (1H, d, J = 7.5 Hz), 7.32 (1H, td, J = 7.5, 2.5 Hz), 7.21 (1H, t, J = 7.5 Hz), 6.78 (2H, BB`part of AA`BB`system), 6.60 (1H, d, J = 1 Hz), 6.50 (1H, s), 5.83 (1H, d, J = 1 Hz), 3.80 (3H, s), 3.72 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 166.8, 164.3, 137.6, 137.4, 135.7, 130.2, 130.0, 129.6, 129.2, 125.8, 124.5, 121.8, 115.6, 114.7, 113.7, 56.2, 52.9; Anal. Calcd. for $C_{19}H_{17}NO_5S$: C, 61.44; H, 4.61; N,3.77. Found: C, 61.57; H, 4.85; N, 3.90.

Diels-Alder reaction of 3. A mixture of **2** (2.72 mmol) and **3** (22.5 mmol) were stirred under reflux for 30 h. Evaporation of the solvent and column purification (Hexane/Ether 1:1) gave **7** (237 mg, 17%) and **8** (376 mg, 27%). **7:** m.p. 85 ^{0}C; ^{1}H-NMR ($CDCl_3$) δ 7.75 (3H, m), 7.38 (1H, d, J = 6.3 Hz), 7.07-7.18 (2H, m), 6.78 (2H, BB`part of AA`BB`system), 6.60 (1H, s), 5.91 (1H, dt, J = 9.0, 3.6 Hz), 5.72 (1H, dd, J = 9.0, 4.5 Hz), 4.85 (1H, d, J = 4.5 Hz), 3.71 (6H, s), 2.75 (1H, dd, J = 13.5, 4.5 Hz), 2.55 (1H, td, J = 13.5, 4.5 Hz), 1.95 (1H, dt, J = 18, 4.5 Hz), 1.25 (1H, tdd, J = 13.5, 18.4, 4.5, 3.6 Hz), 0.21 (9H, s); ^{13}C-NMR ($CDCl_3$) δ 174.6, 163.9, 140.9, 137.8, 131.7 (2C), 130.8, 130.1, 129.5, 127.2, 125.1, 124.1, 121.3, 115.9 (2C), 115.8, 114.5, 70.5, 56.0, 55.3, 52.2, 25.6, 23.3, 1.12 (3C); EIMS m/e 513(2), 498(15), 371(10), 342(100), 226(95). **8**: yellow oil; ^{1}H-NMR ($CDCl_3$) δ 7.70 (2H, AA` part), 7.40-747 (1H, m), 7.07-7.11 (3H, m), 6.81 (2H, BB`part), 6.60 (1H, s), 5.97 (1H, d, J = 10.5 Hz), 5.70 (1H, bd, J = 10.5 Hz), 5.05 (1H, s), 3.84 (3H, s), 3.60 (3H, s), 2.70-2.81 (1H, m), 2.35 (1H, dd, J = 5 8, 13 Hz), 1.89-1.98 (1H, m), 1.70-1.79 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 174.3, 163.8, 132.1 (2C), 131.7, 130.6 (2C), 129.7, 124.7, 124.1, 123.7, 121.3, 120.3, 119.9, 115.9, 115.4, 114.5, 70.5, 56.0,

54.8, 52.2, 31.2, 23.6, 1.5 (3C); Anal. Calcd. for $C_{26}H_{31}NO_6SSi$: C, 60.79; H, 6.09; N, 2.73. Found: (**7**) C, 60.84; H, 6.15; N, 2.88; (**8**) C, 60.94; H, 6.00; N, 2.69.

Diels-Alder reaction of 4. A mixture of **2** (2.72 mmol) and **3** (22.5 mmol) were stirred under reflux for 30 h. Evaporation of the solvent and column purification (Hexane/Ether 3:1) gave **9** (456 mg, 31%) and **10** (280 mg, 19%) as oils. **9:** ^{1}H-NMR ($CDCl_3$) δ 7.80-7.70 (3H, m), 7.41-7.32 (1H, m), 7.20-7.12 (2H, m), 6.85-6.75 (2H, m), 6.65 (1H, s), 5.22 (1H, d, J = 5.4 Hz), 4.43 (1H, d, J = 5.4 Hz), 3.75 (3H, s), 3.65 (3H, s), 3.45 (3H, s), 2.83 (1H, dd, J = 5.4, 13.5 Hz), 2.61 (1H, td, J = 13.5, 5.4 Hz), 2.00-1.81 (1H, m), 1.42-1.20 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 173.5, 163.9, 156.5, 140.6, 138.0, 129.0, 130.0 (2C), 129.2, 125.3, 124.3, 123.9, 121.7, 118.3, 115.9, 114.8, (2C), 101.3, 56.7, 53.0, 52.6, 30.3, 28.0, 26.6, 0.8 (3C). **10**: ^{1}H-NMR ($CDCl_3$) δ 7.74-7.56 (3H, m), 7.46-7.40 (1H, m), 7.18-7.08 (2H, m), 7.04 (1H, s), 6.86-6.74 (2H, m), 5.10-5.17 (1H, m), 4.65 (1H, bs), 3.75 (3H, s), 3.65 (3H, s), 3.35 (3H, s), 2.80-2.72.(1H, m), 2.48-2.31 (1H, m), 2.05-1.87 (1H, m), 1.70-1.55 (1H, m); Anal. Calcd. for $C_{27}H_{33}NO_7SSi$: C, 59.64; H, 6.12; N,2.58. Found: (**9**) C, 59.98; H, 6.25; N, 2.73; (**10**) C, 59.84; H, 6.31; N, 2.79.

11: oil; ^{1}H-NMR ($CDCl_3$) δ 7.75 (1H, d, J = 7.5 Hz), 7.60 (2H, AA' part), 7.40 (1H, d, J = 7.5 Hz), 7.21-7.11 (2H, m), 6.80 (1H, s), 6.75 (2H, BB' part), 4.45 (1H, t, J = 4 Hz), 3.75 (3H, s), 3.70 (3H, s), 3.41 (3H, s), 3.22-3.11 (1H, m), 2.75 (2H, d = 4 Hz), 2.71-2.59 (2H, m), 2.11-1.95 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 208,8, 173.5, 164.1, 142.0, 138.7, 130.1, 129.9 (2C), 129.0 125.8, 124.7, 121.5, 116.4, 115.8, 114.5 (2C), 83.3, 58.3, 56.1, 54.3, 52.9, 42.1, 37.7, 30.2. **12:** oil; ^{1}H-NMR ($CDCl_3$) δ 8.02 (1H, d, J = 7.9 Hz), 7.80 (2H, AA' part), 7.35-7.05 (3H, m), 6.90 (2H, BB' part), 6.21 (1H, s), 4.52 (1H, t, J = 4.5 Hz), 3.80 (3H, s), 3.73 (3H, s), 3.60 (3H, s), 3.35-3.25 (1H, m), 2.80-2.60 (1H, m), 2.40-2.05 (2H, m), 1.40-1.23 (2H, m); Anal. Calcd. for $C_{24}H_{25}NO_7S$: C, 61.13; H, 5.35; N, 2.97. Found: (**11**) C, 61.24; H, 5.51; N, 2.67; (**12**) C, 61.30; H, 5.52; N, 2.64.

13: oil; ^{1}H-NMR ($CDCl_3$) δ 7.70 (2H, AA' part), 7.65-7.55 (1H, m), 7.50-7.40 (1H, m), 7.28 (1H, bd, J = 9 Hz), 7.20-7.11 (2H, m), 6.85 (2H, BB' part), 6.75 (1H, s), 6.22 (1H, d, J = 9 Hz), 3.80 (3H, s), 3.78 (3H, s), 3.10-2.85 (1H, m), 2.82-2.70 (1H, m), 2.68-2.41 (1H, m), 2.40-2.25 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 198.3, 172.9, 164.1, 148.7 (2C), 140.1, 137.9, 131.2, 130.8, 129.8, 128.7, 125.7, 124.3, 121.6, 115.2, 114.8, 114.05 (2C), 56.11, 53.4, 51.5, 34.6, 32.1. Anal. Calcd. for $C_{23}H_{21}NO_6S$: C, 62.85; H, 4.82; N, 3.19. Found: C, 62.77; H, 4.96; N, 3.07.

Diels-Alder reaction of 5. A solution of **2** (6.50 mmol) and **5** (6.50 mmol) were dissolved in toluene (15 ml) and stirred for 72 h. Evaporation of the solvent and column purification (EtOAc/CH_2Cl_2 3:7) gave **14** (1140 mg, 30%) and **15** (228 mg, 6%). **14:** m.p. 175 ^{0}C; ^{1}H-NMR ($CDCl_3$) δ 7.72-7.62 (2H, AA' part), 7.52 (1H, d, J = 8.1 Hz), 7.40-7.13 (6H, m), 7.02 (2H, d, J = 8.1 Hz), 6.90 (2H, BB' part), 6.52 (1H, s), 6.01 (1H, bs), 5.61 (1H, d, J = 16 Hz), 4.61 (1H, s), 3.91 (1H, d, J = 16 Hz), 3.81 (3H, s), 3.60 (3H, s), 2.69-2.49 (5H, m), 2.46-2.33 (1H, m), 2.16-2.03 (1H, m), 1.80-1.60 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 174.0, 173.0, 164.0, 145.0, 138.5, 137.7, 134.4, 132.5, 130.4, 130.2, 129.1 (2C), 128.5 (2C), 128.0 (2C), 127.6, 124.9, 124.3, 121.8, 116.4, 115.1 (2C), 110.2 , 61.9, 56.0, 53.4, 38.2, 47.4, 33.0 (2C), 29.0, 22.1; FABMS m/e 585 (MH^+);. **15:** m.p. 158 ^{0}C; ^{1}H-NMR ($CDCl_3$) δ 7.91 (1H, d, J = 9 Hz), 7.74 (2H, AA' part), 7.39-7.15 (7H, m), 7.01 (1H, t, J = 9 Hz), 6.83 (2H, BB' part), 6.10 (1H, s), 4.95 (1H, d, J = 16 Hz), 4.49 (1H, d, J = 16 Hz), 4.33 (1H, bt, J = 4.5 Hz), 3.78 (3H, s), 3.74 (3H, s), 3.55 (1H, dd, J = 6.0, 7.5 Hz), 2.50-2.41 (2H, m), 2.31-2.18 (2H, m), 2.02-1.70 (2H,m), 1.82-1.72 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 174.0, 169.8, 164.3, 138.9, 138.5, 136.2, 134.2, 130.4, 130.2, 130.0, 129.8 (2C), 128.8 (2C), 128.0 (2C), 126.3, 125.0, 123.2, 122.0, 120.3, 115.0 (2C), 114.1, 56.0, 53.2, 49.2, 41.4, 39.5, 32.1, 27.6, 26.7, 21.0; FABMS m/e 585 (MH^+). Anal. Calcd. for $C_{33}H_{32}O_6N_2S$: C, 67.79; H, 5.52; N, 4.79. Found (**14**) C, 67.66; H, 5.44; N, 4.61; (**15**) C, 66.72; H, 5.66; N, 4.91.

***N*-Benzyl-5-ethenyl-3,4-dihydropyridin-2-one**: To a solution of LDA (2.44 mmol) in THF (20 ml) at -78^0 was added N-benzyl-5-acetyl-3,4-dihydropyridin-2-one (500 mg, 2.2 mmol). After stirring for 2 h TMSCl (0.30 ml, 2.44 mmol) was added and the solution was stirred for 30 min. The solvent was removed and the residue was chromatographed (Hexane/Ether 1:5) to yield **6** (298 mg, 45%). **6:** ^{1}H-NMR ($CDCl_3$) δ 7.30 (5H,

m), 6.45 (1H, s), 4.70 (2H, s), 4.32 (1H, s), 4.21 (1H, s), 2.61 (2H, t, J = 8.1 Hz), 2.50 (2H, t, J = 8.1 Hz), 0.12 (9H, s).

Diels-Alder reaction of 5. A solution of **2** (1 mmol) and **6** (1 mmol) were dissolved in toluene (15 ml) and stirred for 72 h. Evaporation of the solvent and column purification (EtOAc/Hexane 1:1) gave **16** (181 mg, 27%) **16:** ^{1}H-NMR ($CDCl_3$) δ 7.75-7.65 (AA' part), 7.51 (1H, d, J = 8 Hz), 7.41-7.10 (7H, m), 7.01 (1H, d, J = 8 Hz), 6.91 (2H, d, J = 8 Hz), 6.52 (1H, s), 5.64 (1H, d, J = 15.3 Hz), 4.81 (1H, bs), 3.95 (1H, d, J = 15.3 Hz), 3.82 (3H, s), 3.58 (3H, s), 3.00-1.65 (8H, m); FABMS m/e 673 (MH^+).

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