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Stereoselective Syntheses of L-Pipecolic Acid and (2*S*,3*S*)-3-Hydroxypipecolic Acid from a Chiral *N*-Imino-2-phenyl-1,2-dihydropyridine Intermediate

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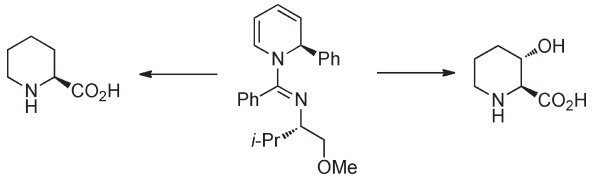

Stereoselective syntheses of L-pipecolic acid and (2*S*,3*S*)-3-hydroxypipecolic acid were achieved from a chiral *N*-imino-2-phenyl-1,2-dihydropyridine intermediate. The 3-hydroxy substituent of the latter amino acid was introduced by hetero-Diels−Alder reaction of singlet oxygen with the 1,2-dihydropyridine.

A metabolite of L-lysine, L-pipecolic acid (**1**, Figure 1) is a naturally occurring nonproteinogenic α-amino acid.[1,2] Numerous natural and synthetic biologically active alkaloids are derived from amino acid **1** or contain it as a key stuctural unit (e.g., amyloglucosidase inhibitor lentiginosine,[3] anticonvulsant pipradol,[4] immunosuppressants FK506,[5] and rapamycin[6]). L-Pipecolic acid and derivatives have been prepared[7] by resolution of the racemates,[1c,8] by synthesis from L-lysine,[9] by diastereoselective[10] and enantioselective syntheses,[11] as well as by deracemization.[12] It has also been recently employed as a catalyst for asymmetric Mannich reactions.[13] (2*S*,3*S*)-3-Hydroxypipecolic acid (**2**) is also of current interest as a synthetic target.[14] The structure of **2** is found in febrifugine,[15] a potential antimalarial agent, and the enantiomer of **2** is found in the structure of the phytotoxin swainsonine.[16] In addition, **1** and **2** are also conformationally constrained amino acids relevant to the study of peptide structure and drug design.[17]

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(17) For reviews, see: (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (b) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785.

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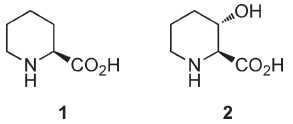
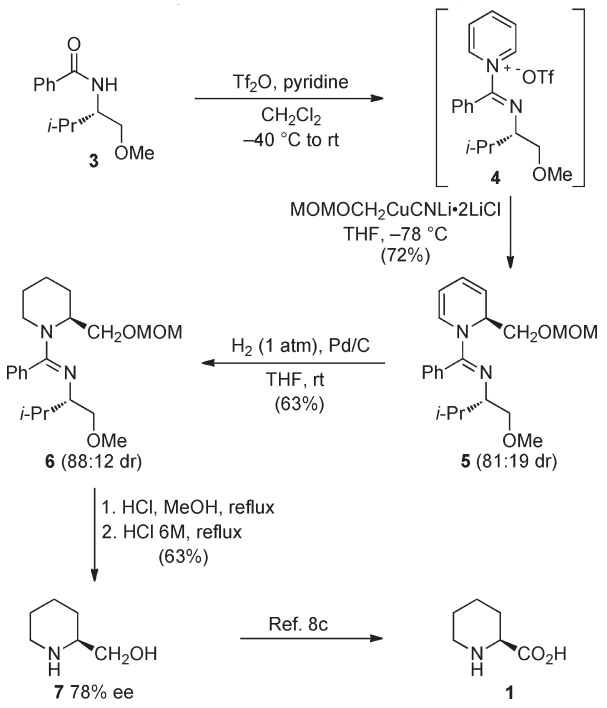


1 **2**

FIGURE 1. L-Pipecolic acid (**1**) and (2*S*,3*S*)-3-hydroxypipecolic acid (**2**).

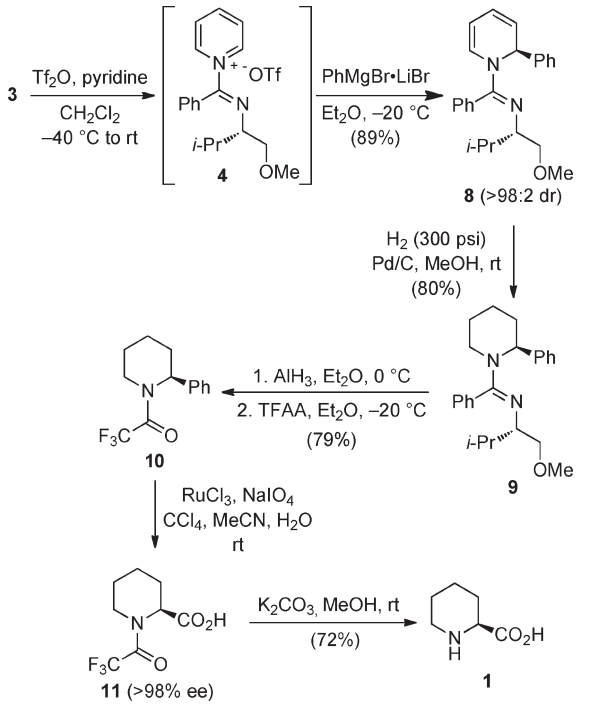
SCHEME 1. Initial Synthesis of L-Pipecolic Acid (1)



We reported a few years ago a novel highly regio- and stereoselective approach to 2-substituted dihydropyridines from unsubstituted *N*-pyridinium salts.[18a] The 1,2-dihydropyridines thus prepared were found to be very useful and versatile intermediates to synthesize enantioenriched substituted piperidines.[18] Our research program directed toward the expedient synthesis of substituted piperidines prompted us to develop a general strategy for the stereocontrolled synthesis of L-pipecolic acid (**1**) and substituted analogues. We report herein efficient syntheses of **1** and the 3-hydroxylated analogue **2**. Our strategy to synthesize L-pipecolic acid was to introduce a carboxylic acid group at the C-2 position of chiral *N*-iminopyridinium salt **4**, preformed by trifluoromethane sulfonic anhydride activation of amide **3** (Scheme 1).[18a]

We first investigated the addition of a protected hydroxymethylene nucleophile as a masked carboxylic acid functionality. Umpolung-type nucleophile $LiCH_2OMOM$ was prepared by a tin−lithium exchange procedure,[19] then further transmetalated in situ before the addition to *N*-iminopyridinium salt **4**.[20] We obtained 1,2-dihydropyridine **5** with the best results observed when the organolithium was transmetalated with a CuCN/LiCl chloride mixture (90:10 ratio of 1,2- vs 1,4-addition and 81:19 diastereoselectivity at C-2). Organomagnesium reagent proved nonregioselective, presumably because the complexation of the nucleophile to the sp^2 nitrogen on **4** was inhibited by possible competing coordination of MOM ether or the tetrahydrofuran solvent needed to effect the tin−lithium exchange. Hydrogenation of dihydropyridine **5** to piperidine **6** occurred with modest yield and slight diastereomeric enrichment. Hydrolysis of both MOM ether protecting group and amidine chiral auxiliary afforded enantioenriched (*S*)-2-piperidine methanol (**7**), therefore completing a formal synthesis of L-pipecolic acid.[8c] Hydrolysis of the MOM ether led to the corresponding primary hydroxyl group, which assisted the hydrolysis of the amidine.[18a,21,22]

SCHEME 2. Optimized Synthesis of L-Pipecolic Acid (1)



We then turned our attention to the introduction of an aromatic substituent, which would be later oxidized to a carboxylic acid with use of the Sharpless procedure.[23] We had success in this strategy with the chiral 2-phenyl-1,2-dihydropyridine **8** (Scheme 2). Dihydropyridine **8** was

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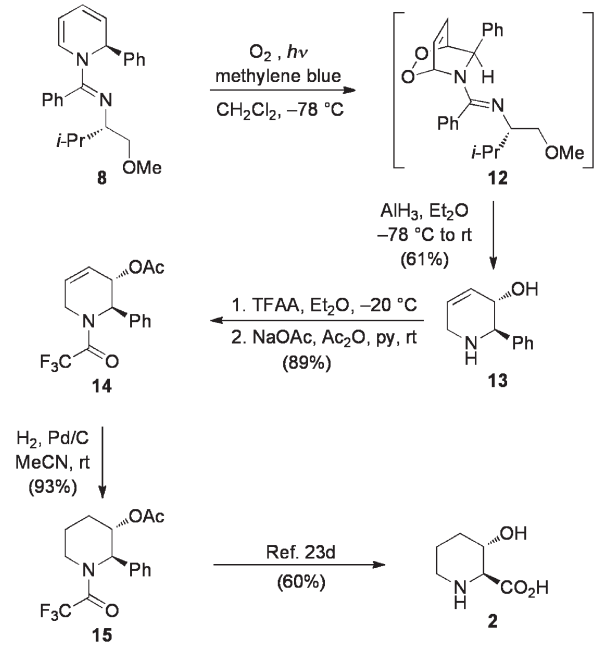
(21) Taguchi, T.; Kasuga, S. *Chem. Pharm. Bull.* **1965**, *13*, 241.

(22) Cyanide addition to the chiral pyridinium salt **4** was also investigated, with limited success. Reaction of **4** with trimethylsilyl cyanide in the presence of aluminum chloride resulted in the formation of a new adduct, which proved too labile for isolation. Chiral amide starting material **3** was recovered, presumably after reversible cyanide liberation and hydrolysis of the pyridinium salt. For related examples, see: (a) Popp, F. D.; Takeuchi, I.; Kant, J.; Hamada, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1765. (b) Yaguchi, K.; Endo, Y. *Tetrahedron Lett.* **1999**, *40*, 7351.

prepared by regio- and diastereoselective addition of phenylmagnesium bromide to chiral pyridinium salt **4**.[18a,24] Hydrogenation of **8** led to the *N*-iminopiperidine **9**.[25] High-pressure hydrogenation ensured a complete hydrogenation, whereas atmospheric hydrogen pressure could be used to effect monohydrogenation to 2-substituted-1,2,3,4-tetrahydropyridines, as reported in our previous communication.[18e] The chiral auxiliary was next removed by alane reduction,[18c,d,26] followed by protection of the piperidine nitrogen as a trifluoroacetamide.[27] Oxidation of the phenyl substituent on **10** unveiled the carboxylic acid group, then the crude *N*-trifluoroacetylpipecolic acid **11** was easily deprotected to afford L-pipecolic acid (**1**).[28] L-Pipecolic acid was thus prepared in 40% yield (6 steps) from **3**, or 30% overall yield (7 steps) from commercially available L-valinol, needed to synthesize **3**.

We planned to use dihydropyridine **8** as a common intermediate in the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**2**). We previously reported a tandem hetero-Diels–Alder (HDA) reaction of nitrosobenzene with 2-substituted *N*-imino-1,2-dihydropyridines, followed by alane reduction.[18d] This methodology allowed for installation of an amino group at C-3 on pyridine ring, trans to the substituent at C-2. To introduce an hydroxy group at C-3 trans to the phenyl substituent, we investigated the HDA reaction of singlet oxygen with **8**.[29] The cycloaddition of singlet oxygen with 2-phenyl-1,2-dihydropyridine **8** proceeded readily (Scheme 3).[30] Unfortunately, the cycloadduct **12** decomposed upon warming to room temperature. We initially attempted sequential tin(II) chloride–sodium cyanoborohydride reduction of the endoperoxide using Natsume's procedure,[29d] with limited success. We found that our typical alane reduction procedure was the best choice for this multiple bond transformation. The endoperoxyde **12** could be efficiently reduced upon transfer of the cold reaction mixture

SCHEME 3. Synthesis of (2*S*,3*S*)-3-Hydroxypipecolic Acid (2)



to an alane suspension, also cooled in an acetone–dry ice bath.

After optimization of the reduction protocol, the tetrahydropyridine **13** was isolated in good yield. Orthogonal protection of piperidine nitrogen and hydroxy group led to **14**, which was hydrogenated to piperidine **15**. This intermediate was previously synthesized (in 14 steps, 8% yield) and transformed into (2*S*,3*S*)-3-hydroxypipecolic acid (**2**).[23d] The synthesis of piperidine **15**, therefore, constitutes a formal synthesis of **2**. Sharpless oxidation of the phenyl substituent followed by piperidine deprotection (K_2CO_3, MeOH) led to (2*S*,3*S*)-3-hydroxypipecolic acid (**2**), as described by Haddad.[23d] The synthesis of **2** required 6 steps from dihydropyridine **8** (30% yield), or 8 steps (20% overall yield) from L-valinol.

In conclusion, we synthesized two different pipecolic acids, L-pipecolic acid (**1**) and (2*S*,3*S*)-3-hydroxypipecolic acid (**2**), from the same 2-phenyl-1,2-dihydropyridine intermediate **8**. The phenyl substituent on the dihydropyridine was used as a masked carboxylic acid group. Introduction of an hydroxy group at the 3-position on the piperidine ring was achieved by using a tandem hetero-Diels–Alder reaction of singlet oxygen with dihydropyridine **8**, followed by alane reduction of the endoperoxide, the aminal as well as the amidine functionalities, in one pot.

Experimental Section

(2*R*,3*S*)-2-Phenyl-1,2,3,6-tetrahydropyridin-3-ol (13). Methylene blue (26 mg, 0.070 mmol) and dihydropyridine **8** (143 mg, 0.398 mmol) were dissolved in dichloromethane (58 mL) and the blue solution was cooled at −78 °C. Oxygen was bubbled through the solution with a needle and the solution was irradiated with a sunlamp (OSRAM Ultra-Vitalux 300W, 230 V) placed ca. 15 cm from the flask. The solution was irradiated for 1 h with a constant oxygen flow. Completion of the hetero-Diels–Alder reaction was monitored by TLC analysis. In a separate flask, lithium aluminum hydride (181 mg, 4.8 mmol)

(23) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. For use in hydroxy amino acid synthesis, see: (b) Shioiri, T.; Matsuura, F.; Hamada, Y. *Pure Appl. Chem.* **1994**, *66*, 2151. For use in pipecolic acid derivatives, see: (c) Nazih, A.; Schneider, M.-R.; Mann, A. *Synlett* **1998**, 1337. (d) Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4231. (e) See ref 14k. (f) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2007**, *63*, 2622.

(24) Regioselectivity of 1,2- vs 1,4-addition, > 98:2; diastereoselectivity of addition at C-2, > 98:2.

(25) Hydrogenation to piperidine failed when a 2-furyl substituent was present at C-2 on the dihydropyridine, instead of the phenyl group shown. The *N*-debenzylation process led to the opening of the piperidine ring if a more electron-rich furan was present at C-2.

(26) Reduction of the amidine chiral auxiliary is readily accomplished with alane (2.5 h). We used the following procedure for alane preparation: Finholt, A. E.; Bond, A. C., Jr.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1947**, *69*, 1199. Using DIBAL-H instead of alane required extensive reaction time in dichloromethane, or refluxing the solution in toluene (4 h) to give similar yield of product.

(27) Following this procedure: Hill, R. K.; Prakash, S. R.; Zydowsky, T. M. *J. Org. Chem.* **1984**, *49*, 1666.

(28) Compound **11** was derived to its methyl ester (**11a**), which allowed for enantiomeric determination. See the Supporting Information.

(29) For precedents on singlet oxygen HDA with dihydropyridines, see: (a) Natsume, M.; Sekine, Y.; Soyagimi, H. *Chem. Pharm. Bull.* **1978**, *26*, 2188. (b) Natsume, M.; Wada, M.; Ogawa, M. *Chem. Pharm. Bull.* **1978**, *26*, 3364. (c) Natsume, M.; Sekine, Y.; Ogawa, M.; Soyagimi, H.; Kitagawa, Y. *Tetrahedron Lett.* **1979**, *20*, 3473. For a precedent with hydride reduction of aminal, see: (d) Utsunomiya, I.; Ogawa, M.; Natsume, M. *Heterocycles* **1992**, *33*, 349.

(30) Singlet oxygen reacted on the less hindered face of the dihydropyridine ring (> 98:2 dr), i.e. anti to the 2-phenyl group (which is forced to be axial by the amidine electron-withdrawing group).

was suspended in ether (5.8 mL), cooled to 0−5 °C by means of an ice−water bath, followed by slow addition of aluminum chloride (4.3 mL of a 0.37 M solution in ether, 1.6 mmol), then the light gray suspension was stirred for 45 min. The freshly prepared AlH_3 suspension was cooled to −78 °C then the solution of endoperoxide cycloadduct at −78 °C was added to the alane suspension via a canula. The resulting suspension was then stirred at −78 °C for 12 h, warmed to room temperature, and stirred for 2 h. The reaction was quenched by slow addition of the suspension to a well-stirred biphasic solution of ether (50 mL), saturated aqueous sodium−potassium tartrate (50 mL), and 2.0 M aqueous sodium hydroxide (2 mL). After 1 h of vigorous stirring, two clear phases were obtained and separated. The aqueous phase was extracted with ether (3 × 10 mL) and organic phases were combined and dried over potassium carbonate. Activated charcoal (1 g) was added to the blue solution; the afforded black mixture was stirred for 5 min and Celite (20 g) was added to the mixture. The suspension was filtered through Celite, the solids were rinsed with dichloromethane, and the filtrate was concentrated under reduced pressure to afford 177 mg of a yellow solid. Flash chromatography of the residue was performed with $MeOH/CH_2Cl_2$ (gradient 2:98−10:90), which afforded 43 mg of **13** (61%) as a white solid: mp 139−140 °C; R_f 0.22 (10:90 $MeOH:CH_2Cl_2$); $[\alpha]^{20}_D$ 58.7 (*c* 1.90, MeOH); ^1H NMR (CD_3OD, 400 MHz) δ 7.44 (br d, J = 7.1 Hz, 2H), 7.37 (td, J = 7.1, 1.6 Hz, 2H), 7.31 (tt, J = 7.2, 1.7 Hz, 1H), 5.91 (ddt, J = 10.2, 4.0, 1.8 Hz, 1H), 5.84 (dq, J = 10.2, 1.8 Hz, 1H), 4.24 (ddq, J = 8.6, 3.5, 2.0 Hz, 1H), 3.51 (ddt, J = 17.3, 3.5, 2.5 Hz, 1H), 3.49 (d, J = 8.5 Hz, 1H), 3.34 (ddt, J = 17.4, 3.6, 1.8 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 143.1 (C), 132.0 (CH), 129.6 (2CH), 129.2 (2CH), 128.8 (CH), 128.5 (CH), 71.1 (CH), 66.2 (CH), 46.5 (CH_2); FTIR (neat) 3600−3000, 3584, 3269, 3091, 3030, 2898, 1649, 1586, 1491, 1288, 1088, 1044, 757, 702 cm^{-1}; LRMS (APCI) calcd for $C_{11}H_{14}NO$ $(M + H)^+$ 176.1, found 176.1. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.08; H, 7.73; N, 7.82. From the same reaction mixture 55 mg (66%) of *N*-benzyl-*N*-[(1*S*)-1-(methoxymethyl)-2-methylpropyl]amine[31] (*N*-benzyl-*O*-methylvalinol) was isolated.

(2*R*,3*S*)-1-Trifluoroacetyl-2-phenyl-1,2,3,6-tetrahydropyridin-3-yl Acetate (14). A suspension of the piperidine **13** (38 mg, 0.22 mmol) in ether (1.0 mL) was cooled to −20 °C, trifluoroacetic anhydride (0.12 mL, 0.18 g, 0.87 mmol) was added, and the resulting solution was stirred for 30 min. The mixture was warmed to room temperature and stirred for 3 h, then the solution was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (3.1 mL), then pyridine (0.88 mL), sodium acetate (90 mg, 1.1 mmol), and acetic anhydride (0.41 mL, 4.3 mmol) were added. The mixture was stirred for 14 h and cooled to 0−5 °C with an ice bath, then saturated aqueous sodium bicarbonate (10 mL) was added. After the mixture was stirred for 30 min, hexane (10 mL) was added, the mixture was transferred to a separatory funnel, and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), then the combined organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure, which afforded 78 mg of a yellow oil. Flash chromatography of the oily residue with EtOAc/hexane (gradient from 0:100 to 15:85) afforded 60 mg (89%) of **14** as a colorless oil: R_f 0.35 (25:75 EtOAc:hexane); $[\alpha]^{20}_D$ +85.6 (*c* 5.03, C_6H_6); ^1H NMR (C_6D_6, 400 MHz) δ (51:49 mixture of rotamers, an asterisk (*) indicates the minor rotamer) 7.09−7.06 (m, 1H + 1H*), 7.01−6.98 (m, 4H + 4H*), 6.26 (s, 1H), 5.81 (ddd, J = 9.9, 5.7, 2.7 Hz, 1H), 5.61−5.57 (m, 1H + 1H*), 5.52 (br d, J = 5.8 Hz, 1H*), 5.34 (s, 1H*), 5.18 (ddd, J = 10.0, 3.9, 2.4 Hz, 1H*), 5.11 (ddd, J = 10.1, 4.4, 2.0 Hz, 1H), 4.64 (ddd, J = 19.8, 3.7, 2.5 Hz, 1*H), 3.82 (br d, J = 18.7 Hz, 1H), 3.06 (ddd, J = 18.9, 4.1, 2.1 Hz, 1H), 3.02 (br d, J = 20.0 Hz, 1H*), 1.65 (s, 3H*), 1.60 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ (51:49 mixture of rotamers, an asterisk (*) indicated the minor rotamer) 170.3 (C + C*), 157.2 (q, J = 35.9 Hz, 1C + C*), 135.8 (C + C*), 130.4 (CH), 129.4 (2C + 2C*), 129.2 (CH*), 128.7 (CH + CH*), 127.8 (CH + CH*), 126.9 (CH + CH*), 123.1 (CH), 121.4 (CH*), 117.7 (q, J = 288 Hz, 1C*), 117.6 (q, J = 288 Hz, 1C), 67.2 (CH*), 66.9 (CH), 58.6 (CH*), 55.7 (CH), 41.4 (q, J = 4.2 Hz, $1CH_2$), 40.6 (CH_2*), 20.7 (CH_3), 20.6 (CH_3*); FTIR (neat) 3063, 3035, 1739, 1694, 1667, 1452, 1234, 1203, 1141, 1023 cm^{-1}; HRMS (ES) calcd for $C_{15}H_{14}F_3NO_3$ $(M + Ag)^+$: 419.9971, found 419.9963. Anal. Calcd for $C_{15}H_{14}F_3NO_3$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.24; H, 4.36; N, 4.50.

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Supporting Information Available: General information, experimental procedures, and characterization data for the synthesis of **1**−**2**, **5**−**7**, **9**−**11**, and **13**−**15**, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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