third ones) or of sulfur and carbon AOs (second one). It is thus expected that for the first and third MOs the relative band intensities will not vary to a large extent on going from HeI to HeII excitation energy, as the decrease due to the contribution of sulfur AOs should be moderated by the increase arising from oxygen AOs. For the band associated with the ionization of the second MO, the important contribution of carbon AOs should temper the expected decrease arising from the participation of the sulfur AO.

These assumptions are in complete agreement with the experimental He I and He II spectra of the model methoxy compound **13** featuring the enol form: for this product, as expected, no dramatic change of the relative band intensities is observed on going from He I to He II excitation energy, except a very slight decrease of the fourth one at 11.72 eV (ionization of a sulfur lone pair) (Figure 3).

On the contrary, for the keto isomer **7**, the decrease of the first band intensity and the invariance of the third one (both associated with π ionizations) may be anticipated. For the second band, attributed to the ionization of the oxygen lone pair, an important intensity increase is forecast. The relative intensity changes observed for the studied compound on going from He I to He II excitation energy are different from the evolution demonstrated for **13** and support our latter expectations in favor of the keto compound **7** (Figure 1): a strong decrease of the first, 8.78-eV band; a weaker decrease of the third, 11.02-eV band; a significant increase of the second, 9.50-eV band (the strong decrease of the fourth, 11.96-eV band, as for the model methoxy isomer **13**, arises from the important contribution of sulfur in a lone pair type MO).

We thus conclude the existence of the keto isomer **7** in the gas phase. The attribution of the spectrum of **8** (for which no He II spectrum could be recorded due to too weak intensity signals) follows from the description of the spectrum of **7** (Figure 2). The alkylthio substitution should bring about a new ionization associated with the antisymmetric combination of the sulfur lone pairs ($n_{S_1} - n_{S_2}$). In agreement with the stabilization expected from the carbonyl lone pair[12] on the experimental IPs (8.2 and 8.8 eV) reported for the 1,1-bis(methylthio)ethylene,[13] the bands associated with the ionizations of the symmetric ($n_{S_1} + n_{S_2}$) and antisymmetric ($n_{S_1} - n_{S_2}$) combinations are thus observed at 8.60 and 9.35 eV, respectively (the first one not very far from the corresponding one of **7** at 8.78 eV). On the other hand, the n_O lone pair ionization should be observed at the same energetic level in **7** and **8**: 9.50 eV. The greater intensity of the 9.35–9.50-eV band of **8** is then accounted for by the attribution of two ionizations arising from the ($n_{S_1} - n_{S_2}$) orbital and from the n_O orbital. Moreover, from the results on the 1,1-bis(methylthio)- and (methylthio)ethylene,[13] it may be anticipated that the ionization related to the ($\pi + n_{S_1} + n_{S_2}$) orbital will be found at a deeper energetic position than for **7** (11.02 eV): indeed for **8** this ionization is hidden in the broad band at 12.34 eV.

The observation of the sole keto isomers of these derivatives of thiophen-3(2*H*)-ones in the gas phase is to be related with the results of their keto–enol equilibrium in solution.

It has been shown that the parent thiophen-3(2*H*)-one (**9**) and its 2,5-dimethyl derivative existed in 75/25 and 90/10 keto/enol mixtures, respectively, in $CHCl_3$ solutions[5,14] and that the percentage of the enol form increased with solvent ability to form hydrogen bonds (100% enol form of **9** in DMSO[14]). On the contrary, compounds **7** and **8** were reported to exist only in the keto form in $CDCl_3$ solutions.[3] We have checked that, for these two latter compounds **7** and **8**, the keto–enol equilibrium was less shifted than for the other previously mentioned thiophen-3(2H)-ones: the keto/enol percentages were found to be 66/34 for **7** and 80/20 for **8** in CD_3COCD_3 and 34/66 and 30/70, respectively, in DMSO-d_6 from NMR spectra. The observation of the keto as the only tautomer for **7** and **8** in $CDCl_3$ bolsters the argument in favor of the identification of the gas-phase species as the keto tautomer since $CDCl_3$, of all the solvents mentioned, is the one most approximating the gas phase (i.e., most lacking in H-bonding ability). It could be pointed out at this stage that, in the MNDO approximation, neglecting correlation effects, the relative energies of the two keto or enol isomers are calculated to be very close (within 1 kcal·mol^{-1}).

In conclusion, compounds **7** and **8** are observed in the keto form both in the gas phase and in $CDCl_3$ solutions.[3] However, the exclusive formation of the cyclic thiophen-3(2*H*)-ones instead of the [(alkylthio)methylene]ketenes from the Meldrum's acid derivatives is a different result from that found in the case of the related methoxy compound: in this latter case, the (methoxymethylene)ketenes were characterized in the gas phase and there was no evidence of furan-3(2*H*)-one formation. Further investigations dealing with these different behaviors are in progress.

Experimental Section

Photoelectron spectra were recorded on an Helectros 0078 photoelectron spectrometer equipped with a 127° cylindrical analyzer and monitored by a microcomputer supplemented with a digital analog converter. The spectra are calibrated on the known ionizations of xenon (12.13 and 13.43 eV) and argon (15.76 and 15.93 eV). The IPs are accurate within 0.02 eV. The short path pyrolysis system has been described elsewhere.[8] The starting Meldrum's acids were synthesized according to the reported methods.[15] The preparations of the thiophen-3(2*H*)-ones[3,5] and 3-methoxythiophene[16] have been described.

Calculations were performed with the AMPAC program[17] on a Vax computer on fully optimized geometries.

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Simple and Convenient Synthesis of *tert*-Butyl Ethers of Fmoc-serine, Fmoc-threonine, and Fmoc-tyrosine

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The protection of the hydroxyl function of serine, threonine, and tyrosine as an acid-labile *tert*-butyl ether is a well-established strategy for the synthesis of polypeptides when using the base-labile 9-fluorenylmethoxycarbonyl (Fmoc) mode of protection for the α-amino

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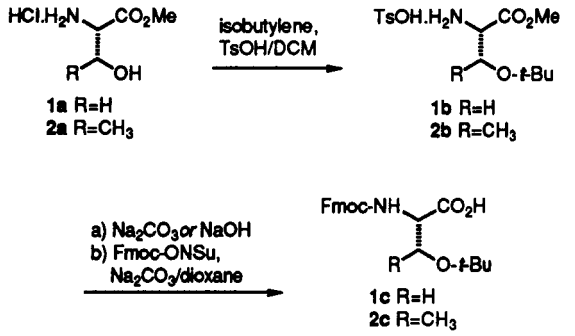
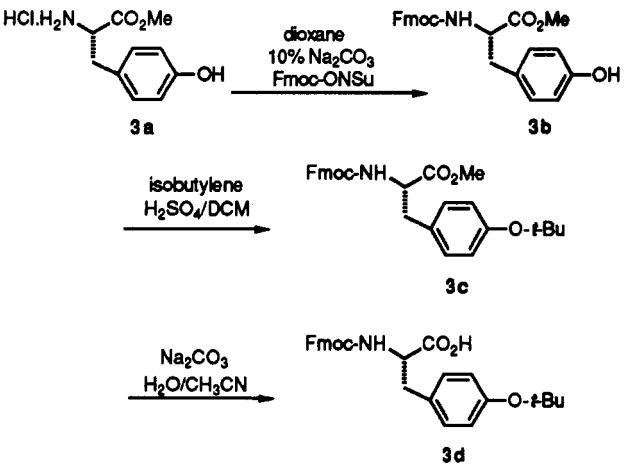
Scheme I



group.[1-3] Although these *N*-Fmoc-*O*-*tert*-butyl amino acids are commercially available, they are expensive and often impure. The reported procedures for the preparation of *N*-Fmoc-*O*-*tert*-butylserine (**1c**), *N*-Fmoc-*O*-*tert*-butylthreonine (**2c**), and *N*-Fmoc-*O*-*tert*-butyltyrosine (**3d**) all require the temporary protection of the carboxylic acid as a benzyl ester[4] or a *p*-nitrophenyl ester[5] which is removed by hydrogenolysis after *tert*-butylation of the hydroxyl function. Carboxyl protection as a methyl ester during *tert*-butylation has been reported,[6] but in conjunction with the benzyloxycarbonyl group for N-protection, which requires hydrogenolysis for its removal. We found these protocols rather tedious and impractical for large-scale synthesis. We report herein rapid and convenient procedures for the synthesis of these diprotected amino acids using a methyl ester as the temporary blocking group for the carboxylic function.

Methyl esters of amino acids were readily available (>97% yield) by esterification with thionyl chloride in methanol.[7] For serine and threonine, *tert*-butylation of the hydroxyl side chain was achieved in high yield by reaction of their corresponding methyl ester hydrochloride in dichloromethane (DCM) in the presence of isobutylene using *p*-toluenesulfonic acid monohydrate (TsOH) as catalyst. Other conditions for the *tert*-butylation reaction, such as sulfuric acid in DCM[8] or other sulfonic acids[9] in DCM, resulted in lower yields. The resulting *O*-*tert*-butyl-L-serine methyl ester was crystallized directly from the reaction mixture as its TsOH salt while the corresponding threonine derivative was crystallized following a quick workup. Hydrolysis with sodium hydroxide generated the free acids. Introduction of the Fmoc group with *N*-[(9-fluorenylmethoxycarbonyl)oxy]succinimide (Fmoc-ONSu)[10,11] could then be carried out in the same reaction flask after addition of Na_2CO_3. By a more expedient procedure, the Fmoc group was introduced following extended mixing of **1b** in 10% Na_2CO_3, which removed the methyl ester. The threonine salt **2b** was not amenable to this latter procedure.

Scheme II



Direct *tert*-butylation of tyrosine methyl ester (**3a**) could not be carried out under any of the above conditions. However, *tert*-butylation of Fmoc-tyrosine methyl ester (**3b**) with isobutylene in DCM in the presence of sulfuric acid gave **3c** in high yield. Hydrolysis of the methyl ester was accomplished with 2% Na_2CO_3 in H_2O/CH_3CN. More basic conditions (0.1 N NaOH or 0.1 N LiOH) resulted in impure product and partial loss of the Fmoc protecting group, while deprotection by *O*-alkyl cleavage methods such as NaCN/HMPA[12] or LiI/DMF[13] failed.

The overall yields for **1c**, **2c**, and **3d** are 85%, 61%, and 60%, respectively, and are substantially better than by previous methods. Melting points, specific rotations, NMR data, and HPLC retention times were comparable to literature values. Enantiomeric purity was confirmed as greater than 99.6% L enantiomer by derivatization with 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide (detection limit less than 0.1% of D enantiomer).[14] Serine and threonine were derivatized following the methyl ester hydrolysis step, whereas tyrosine was tested after removal of both protecting groups from the final product.

In summary, we have found new and mild conditions for the preparation of *tert*-butyl ethers of Fmoc-amino acids by temporary protection of the carboxylic group as the methyl ester and found nonracemizing conditions for the ester hydrolysis. These new procedures should significantly increase access to these useful derivatives.

Experimental Section

***O*-*tert*-Butyl-L-serine Methyl Ester *p*-Toluenesulfonate (1b).** **1a**[7] (10.2 g, 65.7 mmol), TsOH (25.0 g, 131 mmol), and DCM (500 mL) were stirred together under isobutylene gas (5 psi) for 72 h. Alternatively, liquid isobutylene, equal to about one-fifth the volume of DCM, can be used in a thick-walled, well-stoppered flask. Following careful degassing, evaporation to $^1/_3$ volume, and addition of Et_2O (2.5 L), chilling yielded white crystals: 20.2 g (89%); mp 141–142°C; $[\alpha]^{20}_D$ +13.0° (c = 1.0, DMF); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 9 H, $C(CH_3)_3$), 2.33 (s, 3 H, CH_3), 3.71 (s, 3 H, OCH_3), 3.83 (ddd, J = 18.1, 8.2, 3.0 Hz, 2 H, β,β'-H), 4.31 (t, J = 3.0 Hz, 1 H, α-H), 7.14 (d, J = 8.0 Hz, 2 H, H_{arom}), 7.72 (d, J = 8.1 Hz, 2 H, H_{arom}). Anal. Calcd for $C_{15}H_{25}NO_6S$: C, 51.85; H, 7.27; N, 4.03; S, 9.23. Found: C, 51.89; H, 7.39; N, 4.04; S, 9.37.

***O*-*tert*-Butyl-L-threonine Methyl Ester *p*-Toluenesulfonate (2b).** **2b** was prepared from **2a**[7] (2.00 g, 11.8 mmol) in DMC (100 mL) as described for **1b**, except that 5 equiv of TsOH (11.2 g, 58.9 mmol) was necessary to drive the *tert*-butylation in

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good yield. Following evaporation to $^1/_3$ volume, the reaction solution was quickly washed with cold, saturated $NaHCO_3$ (50 mL), dried (Na_2SO_4), and evaporated to 5 mL. Addition of 30–60 °C petroleum ether (150 mL) precipitated a white solid: 2.85 g (67%); mp 130–131 °C; $[\alpha]^{20}_D$ +5.5° (c = 1.0, DMF); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09 (s, 9 H, $C(CH_3)_3$), 1.28 (d, J = 6.4 Hz, 3 H, γ-CH_3), 2.34 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 3.85 (d, J = 2.6, 1 H, α-H), 4.13 (dq, J = 6.4, 2.5 Hz, 1 H, β-H), 7.13 (d, J = 8.0 Hz, 2 H, H_{arom}), 7.77 (d, J = 8.1 Hz, 2 H, H_{arom}). Anal. Calcd for $C_{16}H_{27}NO_6S$: C, 53.16; H, 7.54; N, 3.87; S, 8.87. Found: C, 53.11; H, 7.49; N, 3.81; S, 9.11.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-*tert*-butyl-L-serine (1c). Procedure 1.** **1b** (10.0 g, 28.8 mmol) was stirred in 10% Na_2CO_3 (200 mL) at rt for 24 h and chilled (0 °C) and Fmoc-ONSu (10.2 g, 30.2 mmol) in p-dioxane (100 mL) added dropwise. After 24 h of stirring and gradual warming to rt, the mixture was washed with Et_2O (3 × 100 mL) and the aqueous phase chilled (0 °C), acidified with concd HCl to pH 2, and then extracted with Et_2O (3 × 100 mL). The combined Et_2O extracts were dried (Na_2SO_4) and evaporated to an oil, which gave white crystals from CH_3NO_2: 10.5 g (95%); mp 128.5–130 °C (lit.[4] mp 126–129 °C); $[\alpha]^{20}_D$ +26.7° (c = 1.0, EtOAc) (lit.[4] $[\alpha]^{23-25}_D$ +25.4° (c = 1.0, EtOAc)); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (s, 9 H, $C(CH_3)_3$), 3.76 (dd, J = 8.5, 5.5 Hz, 1 H, β-H), 4.12 (dd, J = 8.8, 3.1 Hz, 1 H, β'-H), 4.43 (t, J = 7.0 Hz, 1 H, CH_{Fmoc}), 4.5–4.6 (m, 3 H, α-H, CH_{2Fmoc}), 5.82 (d, J = 7.6 Hz, 1 H, NH), 7.4–8.0 (m, 8 H, H_{arom}). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.90; H, 6.58; N, 3.65. Found: C, 68.99; H, 6.50; N, 3.71.

Procedure 2. A solution of **1b** (2.00 g, 5.75 mmol) and NaOH (0.46 g, 11.5 mmol) in water (50 mL) was stirred at 0 °C for 2 h and then neutralized with concd HCl. Na_2CO_3 was added to 10% (w/v). Derivatization with Fmoc-ONSu (2.04 g, 6.04 mmol), workup, and crystallization were carried out as in procedure 1, yielding white crystals: 2.10 g (95%); mp 129–130.5 °C; $[\alpha]^{20}_D$ +25.9° (c = 1.0, EtOAc); NMR as above.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-*tert*-butyl-L-threonine (2c).** **2b** (0.58 g, 1.61 mmol) was hydrolyzed with NaOH (0.13 g, 3.22 mmol) and derivatized with Fmoc-ONSu (0.57 g, 1.69 mmol) as described in procedure 2, providing white crystals: 0.58 g (91%); mp 131–132 °C (lit.[4] mp 129–132 °C); $[\alpha]^{20}_D$ +15.3° (c = 1.0, EtOAc) (lit.[4] $[\alpha]^{23-25}_D$ + 15.5° (c = 1.0, EtOAc)); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (d, J = 6.1 Hz, 3 H, γ-CH_3), 1.32 (s, 9 H, $C(CH_3)_3$), 4.21 (t, J = 7.0 Hz, 1H, CH_{Fmoc}), 4.31 (m, 2 H, α-H, β-H), 4.40 (d, J = 7.0 Hz, 2 H, CH_{2Fmoc}), 5.72 (br s, 1 H, NH), 7.2–7.8 (m, 8 H, H_{arom}). Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.49; H, 6.86; N, 3.52. Found: C, 69.47; H, 6.74; N, 3.31.

***N*-(9-Fluorenylmethoxycarbonyl)-L-tyrosine Methyl Ester (3b).** Fmoc-ONSu (37.4 g, 95.0 mmol) in p-dioxane (160 mL) was added dropwise to **3a**[7] (20.0 g, 86.3 mmol) in a mixture of 10% Na_2CO_3 (170 mL) and p-dioxane (80 mL) at 0 °C. After 20 h of stirring with gradual warming to rt, the solution was poured into ice/water (1.3 L) and extracted with Et_3O (3 × 400 mL). The extract was washed with brine (500 mL), dried (Na_2SO_4), and evaporated to an oil, which crystallized from EtOAc/hexane: 35.0 g (97%); mp 122–125 °C; $[\alpha]^{20}_D$ −17.0° (c = 1.0, DMF); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.9–3.2 (m, 2 H, β-CH_2), 3.72 (s, 3 H, OCH_3), 4.20 (t, J = 6.9 Hz, 1 H, CH_{Fmoc}), 4.3–4.7 (m, 3 H, CH_{2Fmoc}, α-H), 5.28 (d, J = 8.2 Hz, 1 H, NH), 5.69 (br s, 1 H, OH), 6.73 (d, J = 8.3 Hz, 2 H, $H_{tyr,arom}$), 6.94 (d, J = 8.3 Hz, 2 H, $H_{tyr,arom}$), 7.3–7.8 (m, 8 H, $H_{Fmoc,arom}$). Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.92; H, 5.56; N, 3.36. Found: C, 71.85; H, 5.71; N, 3.02.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-*tert*-butyl-L-tyrosine Methyl Ester (3c).** **3b** (5.00 g, 12.0 mmol), concd H_2SO_4 (0.33 mL, 6.0 mmol), and DCM (100 mL) were stirred under isobutylene gas (5 psi) for 6 h at rt. The solution was washed with cold 10% $NaHCO_3$ (2 × 100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in 1:1 MeOH/CCl_4 (400 mL), washed with water (300 mL), and then extracted with 1:1 MeOH/water (2 × 200 mL). The extract was dried (Na_2SO_4) and evaporated to a white solid, which was recrystallized from DCM/hexane: 4.70 g (83%); mp 90–92 °C; $[\alpha]^{20}_D$ −22.1° (c = 1.0, DMF); ^{1}H NMR ($CDCl_3$, 200 MHZ) δ 1.32 (s, 9 H, $C(CH_3)_3$), 3.07 (d, J = 5.8 Hz, 2 H, β,β'-CH_2), 3.70 (s, 3 H, OCH_3), 4.21 (t, J = 6.8 Hz, 1 H, CH_{Fmoc}), 4.3–4.6 (m, 3 H, CH_{2Fmoc}, α-H), 5.24 (d, J = 8.1 Hz, 1 H, NH), 6.90 (d, J = 8.4 Hz, 2 H, $H_{tyr,arom}$), 6.98 (d, J = 8.4 Hz, 2 H, $H_{tyr,arom}$), 7.3–7.8 (m, 8 H, $H_{Fmoc,arom}$). Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.54; H, 6.61; N, 2.96. Found: C, 73.49; H, 6.64; N, 3.15.

***N*-(9-Fluorenylmethoxycarbonyl)-*O*-*tert*-butyl-L-tyrosine (3d).** A mixture of **3c** (2.00 g, 4.22 mmol) in CH_3CN (250 mL) and 3% Na_2CO_3 (375 mL) was stirred for 15 h, then washed with hexane (3 × 500 mL), acidified with 2 N HCl to pH 3–4, and extracted with $CHCl_3$ (2 × 600 mL). The combined $CHCl_3$ fractions were washed with brine (500 mL), dried (Na_2SO_4), and evaporated to an oil, which gave white crystals from EtOAc/hexane: 1.43 g (74%); mp 150–151 °C (lit.[4] mp 150–151 °C); $[\alpha]^{20}_D$ −28.0° (c = 1.0, DMF) (lit.[4] $[\alpha]^{23-25}_D$ −27.6° (c = 1.0, DMF)); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 9 H, $C(CH_3)_3$), 2.9–3.2 (m, 2 H, β,β'-CH_2), 4.20 (t, J = 6.8 Hz, 1 H, CH_{Fmoc}), 4.3–4.5 (m, 2 H, CH_{2Fmoc}), 4.6–4.7 (m, 1 H, α-H), 5.22 (d, J = 8.0 Hz, 1 H, NH), 6.90 (d, J = 8.2 Hz, 2 H, $H_{tyr,arom}$), 7.03 (d, J = 8.2 Hz, 2 H, $H_{tyr,arom}$), 7.3–7.8 (m, 8 H, $H_{Fmoc,arom}$). Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.17; H, 6.37; N, 3.05. Found: C, 73.29; H, 6.48; N, 2.85.

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Registry No. **1a**, 5680-80-8; **1b**, 132776-33-1; **1c**, 71989-33-8; **2a**, 39994-75-7; **2b**, 132776-34-2; **2c**, 71989-35-0; **3a**, 3417-91-2; **3b**, 82911-79-3; **3c**, 132409-94-0; **3d**, 71989-38-3; $Me_2C{=}CH_2$, 115-11-7; Fmoc-ONSu, 82911-69-1.

Synthesis of a New Family of Chiral Fluorinated Synthons: (*R*)- and (*S*)-4-Fluoro-1-alkynes

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The synthesis and use of fluorinated biomolecules is currently an area of intense research.[1] Useful optically pure synthons bearing a chiral fluoromethylene group remain relatively rare although substantial progress has been reported recently.[2] In connection with ongoing mechanistic studies in the area of fatty acid biomodification,[3] we required a general synthesis of chiral fluorinated fatty acids. We were also spurred on by reports of new ferroelectric liquid crystalline materials bearing a pendant chiral fluoroalkyl chain.[4] We now report a facile multigram synthesis of a chiral monofluorinated terminal alkyne. In addition, we have been able to prepare the corresponding chiral 3-fluoro carboxylic acids by permanganate oxidation of the title compounds.

Results and Discussion

Our synthetic route is based on the availability of chiral homopropargyl alcohols whose configuration has been unambiguously determined.[5a,b] (See Scheme I.) Thus racemic 1-decyn-4-ol, prepared by reaction of lithium

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