SYNTHESIS OF AN AMINOPYRAZOLIDINE SUBSTITUTED QUINOLONE ACID

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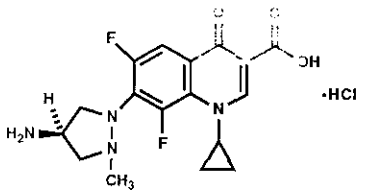
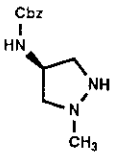
Abstract——A synthesis of a new heterocycle, 2-methyl-4-(S)-Cbz-aminopyrazolidine (**2**), and the preparation of aminopyrazolidine substituted quinolone acid **1** are reported.

In our continuing search for new quinolone acid antibacterial agents, we became interested in novel C-7 heterocyclic substituents.[1] Herein we report the synthesis of (S)-2-methyl-4-(S)-benzyloxycarbonylaminopyrazolidine (**2**) and its reaction with 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (3) to provide, after deprotection, the targeted compound 1-cyclopropyl-6,8-difluoro-7-(4-(R)-amino-2-methylpyrazolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (**1**, U-83140A).

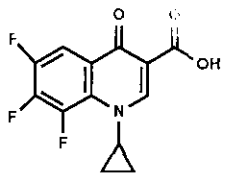
For the synthesis of quinolone acid U-83140A, we have developed a synthesis of aminopyrazolidine **2** as a trifluoroacetate salt (Scheme I and II) which uses Vederas' β-lactone **5**, prepared according to his procedure,[2] as a starting material. This lactone was reacted with methylhydrazine to obtain hydrazide **6**. No regioisomer of **6** was observed in this reaction.



1 (U-83140A)



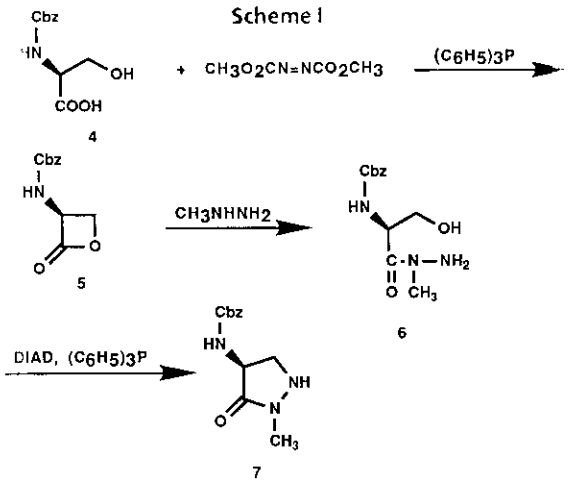
2



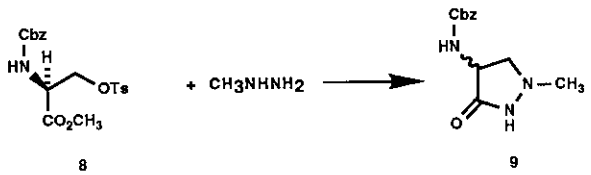
3

It is known that activated acyl groups such as acyl halides and anhydrides generally react at the more substituted nitrogen atom of an unsymmetric alkylhydrazine while less activated acyl compounds such as esters react at the less substituted nitrogen.[3] We expected that the acyl group of β-lactone **5** would be activated enough to prefer reaction at the more substituted nitrogen of methylhydrazine to produce hydrazide compound **6**. This hydrazide **6** was cyclized under Mitsunobu reaction conditions to give pyrazolidinone **7**.

Scheme I



To unequivocally prove the regiochemistry of **7**, we also prepared the other isomer, **9**, from tosylated serine **8**. It is known from similar studies that the pyrazolidinone formed under these reaction conditions is racemic.[4]



The chemical shift differences in the proton and ^{13}C nmr spectra of compounds **7** and **9** shown below clearly confirmed the assigned structures. The carbon and proton shifts of **9** are more amine-like than amide-like as shown by comparison to dimethylformamide and trimethylamine. Furthermore, the C-5

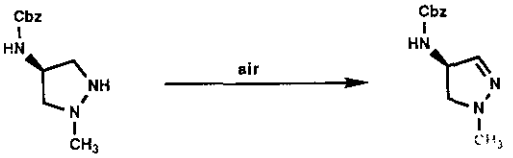
Compounds		7	9
^1H nmr ($CDCl_3$, δ)	N-CH_3	3.06	2.62
^{13}C nmr ($CDCl_3$, δ)	N-CH_3	31.8	47.1
^{13}C nmr ($CDCl_3$, δ)	C-5-CH_2	51.4	60.0

methylene carbon of **9** resonates 8.6 ppm downfield from the corresponding carbon of **7** which is reasonable for a methylene with an additional β-methyl substituent.

Attempts to reduce the pyrazolidinone carbonyl of **7** under various reduction conditions failed. We felt that the difficulty of this reaction stems from the free hydrogen of the pyrazolidinone ring N-H. Therefore, we blocked that nitrogen with a *t*-BOC group and proceeded with a sodium borohydride reduction.

Unlike the similar isoxazolidinone case,[1] the reduction of **10** produced the acyclic compound **11** instead of pyrazolidine **12**. This may well be due to the much diminished basicity of the lone pairs of the methylated nitrogen atom.

Acyclic compound **11** was cyclized under Mitsunobu reaction conditions to obtain *t*-BOC protected pyrazolidine **12**. Deprotection of the *t*-BOC group with trifluoroacetic acid yielded pyrazolidine **13** as its TFA salt. We tried to prepare a TFA-free pyrazolidine by treating **13** with base, but the free pyrazolidine compound was too sensitive to air oxidation which produced unsaturated pyrazolidinene **14**. Therefore, we decided to use the acid salt directly in the coupling reaction with quinolone **3**.



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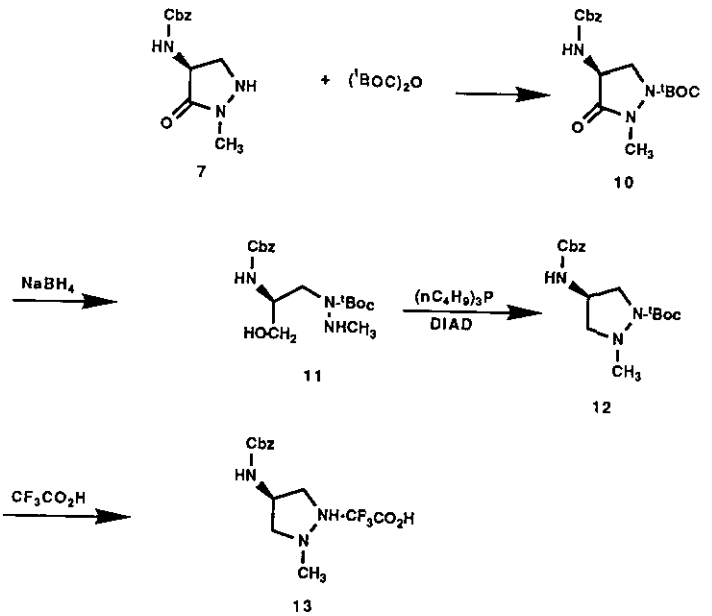
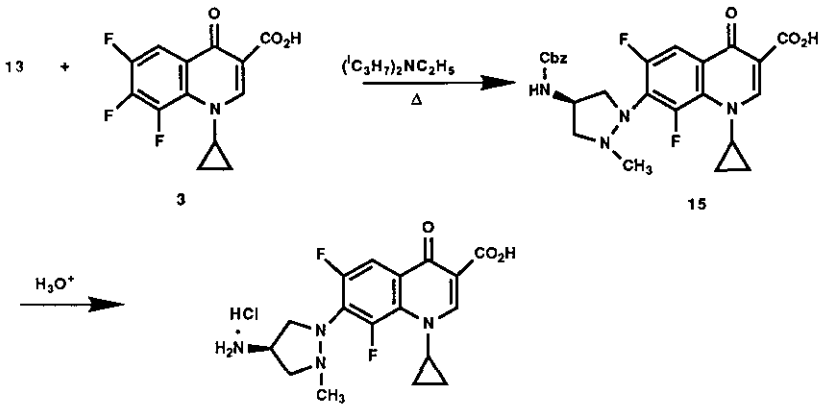
Scheme II



7 10 11 12 13



The coupling reaction in the presence of Hünig's base under rigorously airless conditions, using deoxygenated dimethyl sulfoxide, occurred smoothly to provide compound **15**. Deprotection of the benzyloxycarbonyl group (Cbz) by acidic hydrolysis produced the final quinolone antibiotic **1**, U-83,140A.

Quinolone antibiotic U-83140A demonstrates a potent antibacterial activity. However, its activity was weaker than an aminoisoxazolidine containing quinolone acid U-82662A.[1]

EXPERIMENTAL

General experimental details for this work were described previously.[1]

Synthesis of N-Cbz-(L)-serine-(1-methyl) hydrazide (6).

A slurry of β-lactone **5** (4.60 g, 20.8 mmol) in methylene chloride (50 ml) was cooled to 0°C. To this mixture were added methylhydrazine (1.2 ml, 22.0 mmol) and additional methylene chloride (5 ml). The mixture initially became homogeneous, then heterogeneous again and after 75 min, it was allowed to warm to room temperature. It was concentrated *in vacuo* to one-third volume. The residue was triturated with 1:1/ether:hexane (30 ml) which resulted in the precipitation of the desired product. This precipitated solid was filtered, washed with 1:1/ether:hexane and dried to obtain white pure solid hydrazide **6** (5.33 g, 96%), mp 114-116°C; ^{1}H nmr (DMSO-d_6) δ: 7.40-7.28 (m, 5H), 6.86 (d, J = 8.8 Hz, 1H), 5.08-4.97 (broad, 1H), 5.01 (s, 2H), 4.79 (s, 2H), 4.80-4.68 (m, 1H), 3.70-3.61 (m, 1H), 3.59-3.48 (m, 1H), 2.99 (s, 3H); ^{13}C nmr (DMSO-d_6) δ: 171.1 (s), 155.6 (s), 137.0 (s), 128.2 (d), 127.6 (d), 65.1 (t), 61.3 (t), 53.7 (d), 37.5 (q); ir (neat) cm^{-1}: 3327, 1708, 1661, 1526, 1235, 1060; hrms: (m/z) calcd for $C_{12}H_{17}N_3O_4$: 267.1219; found: 267.1220.

2-Methyl-4-(S)-Cbz-aminopyrazolidin-3-one (7).

Diisopropyl azodicarboxylate (1.98 ml, 10.1 mmol) was added slowly (10 min) to a cloudy mixture of hydrazide **6** (2.08 g, 7.79 mmol) and triphenylphosphine (2.65 g, 10.1 mmol) in tetrahydrofuran (80 ml) at room temperature. After 35 min the mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on medium silica gel, eluting with 1:1/methylene chloride:ethyl acetate containing methanol with a gradient of 0-6%. The fractions containing the desired product were combined and concentrated *in vacuo*. The solid residue was washed with 2:1/ether:hexane and dried to obtain white solid pyrazolidinone **7** (1.64 g, 84%), mp 155-156°C; ^{1}H nmr ($CDCl_3$) δ: 7.41-7.29 (m, 5H), 5.55-5.44 (broad, 1H), 5.11 (s, 2H), 4.37-4.27 (m, 1H), 3.85 (dd, J = 11.3, 11.2 Hz, 1H), 3.14 (dd, J = 11.3, 11.3 Hz, 1H), 3.07 (s, 3H); ^{13}C nmr ($CDCl_3$) δ: 169.4 (s), 156.5 (s), 136.0 (s), 128.6 (d), 128.2 (d), 128.1 (d), 67.1 (t), 53.4 (d), 51.4 (t), 31.8 (g); ir (neat) cm^{-1}: 3223, 3059, 1727, 1673, 1559, 1287, 1254; hrms: (m/z) calcd for $C_{12}H_{15}N_3O_3$ [m/z] + : 249.1113; found: 249.1125.

1-Methyl-4-Cbz-aminopyrazolidin -3-one (9).

Methylhydrazine (6.58 ml, 121.1 mmol) was added to a solution of tosylate **8** (16.45 g, 40.37 mmol) in methylene chloride (100 ml) at 0°C. After 4 h at 0°C the mixture which had become heterogeneous was filtered. The filtrate was concentrated and the residue was purified by flash column chromatography on medium silica gel, eluting with 1:1/methylene chloride:ethyl acetate containing a gradient of methanol from 5-10%. The product containing fractions were combined and concentrated and the solid residue was washed with ether then with hexane to obtain white solid pyrazolidinone **9** (7.63 g, 76%), mp 129-131°C; ^{1}H nmr ($CDCl_3$) δ: 7.40-7.29 (m, 5H), 6.49-6.29 (br, 1H), 5.30 (s, 2H), 4.78-4.65 (m, 1H), 3.67-3.50 (m, 1H), 3.25-3.08 (br, 1H), 2.62 (s, 3H); ^{13}C nmr ($CDCl_3$) δ: 173.0 (s), 156.8 (s), 136.2 (s), 128.5 (d), 128.2 (d), 67.1 (t), 60.0 (t), 50.4 (d), 47.1 (q); ir (neat) cm^{-1}: 3236, 1700, 1538, 1455, 1271, 1252; hrms: (m/z) calcd for $C_{12}H_{15}N_3O_3$ [m/z] + : 249.1113; found 249.1122.

1-*t*-BOC-2-methyl-4-(S)-N-Cbz-aminopyrazolidin -3-one (10).

A mixture of pyrazolidinone **7** (590 mg, 2.4 mmol), di-*t*-butyl dicarbonate (540 mg, 2.5 mmol), pyridine (5 ml) and methylene chloride (5 ml) was stirred at room temperature for 2 h. The mixture was heated at reflux temperature for 6 h and was then allowed to cool to room temperature and stirred for an additional 65 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on medium silica gel, eluting with methylene chloride, containing ethyl acetate with a gradient of 2.5%-50%, then with 5% methanol in 1:1/methylene chloride:ethyl acetate. The product containing fractions were concentrated *in vacuo* to obtain pyrazolidinone **10** as an oil (540 mg, 62%). The fractions containing starting pyrazolidinone **7** were concentrated and the solid residue was washed with ether and dried to recover starting material (17.8 mg, 30%); ^{1}H nmr ($CDCl_3$) δ: 7.40-7.30 (m,

5H), 5.42-5.36 (broad, 1H), 5.12 (s, 2H), 4.72 (dd, J = 11.3, 11.3 Hz, 1H), 3.25 (s, 3H), 1.51 (s, 9H); ^{13}C nmr ($CDCl_3$) δ: 168.9 (s), 156.5 (s), 156.2 (s), 136.0 (s), 128.6 (d), 128.3 (d), 128.1 (d), 83.3 (s), 67.3 (t), 54.8 (t), 51.2 (d), 33.7 (q), 28.1 (q); ir (neat) cm^{-1}: 2978, 1710, 1530, 1455, 1426, 1370, 1322, 1249, 1157; hrms (FAB): calcd for $C_{17}H_{23}N_3O_5$ [M + H] + : 350.1716; found: 350.1694.

2-(S)-Cbz-amino-3-(2-methyl-1-*t*-BOC)-hydrazinopropanol (**11**).

A solution of pyrazolidinone **10** (1.85 g, 530 mmol) in absolute ethanol (35 ml) was cooled to 0°C. Solid sodium borohydride (601 mg, 15.9 mmol) was added to the mixture and after 2 h it was allowed to warm to room temperature. After another 16 h the reaction mixture was cooled to 0°C and glacial acetic acid was added to it slowly until gas evolution ceased. Methanol was added to the very thick reaction mixture and it was stirred until the reaction mixture became a homogeneous solution. It was concentrated *in vacuo* and the residue was co-evaporated with methanol three times and was then partitioned between methylene chloride and water. The organic layer was taken and the aqueous layer was extracted three times with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography on medium silica gel, eluting with methylene chloride with a gradient of 20-50% ethyl acetate. The product containing fractions were concentrated *in vacuo* to obtain hydrazine **11** as an oil (1.68 g, 90%); ^1H nmr (CD_3OD) δ: 7.39-7.24 (m, 5H), 5.05 (s, 2H), 4.02-3.93 (m, 1H), 3.55 (d, J = 5.2 Hz, 1H), 3.55-3.44 (m, 1H), 3.41-3.32 (m, 1H), 2.51 (s, 3H), 1.45 (s, 9H); ^{13}C nmr (CD_3OD) δ: 158.5 (s), 157.7 (s, broad), 138.2 (s), 129.4 (d), 129.0 (d), 128.9 (d), 82.1 (s), 67.5 (t), 63.3 (t), 53.2 (d), 50.5 (t, broad), 36.7 (q, broad), 28.6 (q); ir (neat) cm^{-1}: 3437, 2976, 2934, 1691, 1454, 1425, 1395, 1367, 1343, 1157; hrms (FAB): calcd for $C_{17}H_{27}N_3O_5$ [m + H] + : 354.2029; found: 354.2009.

1-*t*-BOC-2-methyl-4-(R)-Cbz-amino-pyrazolidine (**12**).

To a solution of hydrazide **11** (1.30 g, 3.68 mmol) and tributylphosphine (1.18 ml, 4.53 mmol) in THF (35 ml) was added diisopropyl azodicarboxylate (0.92 ml, 4.56 mmol) at room temperature dropwise over a five minute period. After 2 h the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on medium silica gel eluting with hexane:methylene chloride:ethyl acetate with a gradient of 3:2:1-1:1:2. The product containing fractions were combined and concentrated *in vacuo*. The white solid residue was washed with hexane to obtain pyrazolidine **12** (0.95 g, 76%), mp 84-87°C; ^1H nmr ($CDCl_3$) δ: 7.40-7.28 (m, 5H), 5.17-5.02 (broad, 1H), 5.10 (s, 2H), 4.60-4.49 (m, 1H), 3.76 (dd, J = 11.5, 6.8 Hz, 1H), 3.49 (dd, J = 11.5, 6.1 Hz, 1H), 3.01 (dd, J = 11.5, 5.4 Hz, 1H), 2.63 (s, 3H), 1.47 (s, 9H); ^{13}C nmr (CD_3OD) δ: 158.1 (s), 155.8 (s), 138.0 (s), 129.4 (d), 129.0 (d), 128.8 (d), 81.8 (s), 67.4 (t), 60.6 (t), 52.1 (d), 50.9 (t), 45.3 (q), 28.6 (q); ir (neat) cm^{-1}: 3310, 2975, 1690, 1536, 1455, 1417, 1392, 1366, 1254, 1156, 1111, 1025; hrms (m/z): calcd for $C_{17}H_{25}N_3O_4$ [m/z] + : 335.1845; found: 335.1855.

1-Methyl-4-(S)-Cbz-Aminopyrazolidine trifluoroacetate (13).

A solution of pyrazolidine **12** (197 mg, 0.58 mmol) in methylene chloride (4 ml) was cooled to 0°C, and to the mixture was added trifluoroacetic acid (4 ml). After 10 min the mixture was allowed to warm to room temperature, and after 3.5 h it was concentrated *in vacuo* to obtain pyrazolidine **13** as an oil (200 mg, 97%); ^{13}C nmr (CD_3OD) δ: 7.42-7.27 (m, 5H), 5.10 (s, 2H), 4.54-4.42 (m, 1H), 3.62 (dd, J = 12.2, 7.4 Hz, 1H), 3.52-3.42 (m, 1H), 3.39-3.31 (m, 1H), 3.27 (dd, J = 12.2, 4.1 Hz, 1H), 2.98 (s, 3H); ^{13}C nmr CD_3OD) δ: 158.3 (s), 138.0 (s), 129.5 (d), 129.1 (d), 128.9 (d), 67.8 (t), 62.0 (t), 52.9 (d), 52.8 (t), 42.8 (q).

1-Cyclopropyl-6,8-difluoro-7-(4-(R)-Cbz-amino-2-methylpyrazolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (15).

A mixture of TFA salt **13** (2.5 mmol, assuming quantitative deprotection of **12**), quinolone carboxylic acid **3** (260 mg, 0.92 mmol) and N,N-diisopropylethylamine (0.78 ml, 4.4 mmol) in deoxygenated (degassed then saturated with dry nitrogen) dimethyl sulfoxide (6 ml) was heated to 85-90°C. After 25 h at that temperature, the mixture was concentrated *in vacuo* and the residue was triturated with 1:1:2/ acetonitrile:ethyl acetate:ether which resulted in the precipitation of the desired product. This precipitated solid product was filtered, washed with ether, and dried to obtain pure quinolone **15** (268 mg, 59%), mp 152-155°C; ^{1}H nmr ($CDCl_3$) δ: 14.60 (broad, 1H), 8.69 (s, 1H), 7.83 (d, J = 11.9 Hz, 1H), 7.32 (s, 5H), 5.41 (d, J = 7.3 Hz, 1H), 5.09 (s, 2H), 4.82-4.69 (broad, 1H), 4.16-4.06 (m, 1H), 4.05-3.94 (m, 1H), 3.50-3.39 (m, 1H), 3.31 (dd, J = 11.6, 6.8 Hz, 1H), 3.12 (dd, J = 11.6, 5.6 Hz, 1H), 2.64 (s, 3H), 1.37-1.10 (m, 4H); ^{13}C nmr (DMSO-d_6) δ: First the proton multiplicities based on a DEPT experiment are given, followed by any multiplicity caused by fluorine coupling observed in the proton decoupled spectrum, 175.7 (s), 165.3 (s), 155.8 (s), 152.5 (s) (d, J_{CF} = 252 Hz), 150.1 (d), 144.0 (s) (dd, J_{CF} = 257, 6Hz), 136.8 (s), 133.6 (s) (dd, J_{CF} = 11, 11Hz), 128.5 (s) (d, J_{CF} = 6 Hz), 128.3 (d), 127.8 (d), 119.6 (s) (d, J_{CF} = 9 Hz), 106.6 (d) (d, J_{CF} = 24 Hz), 106.4 (s), 65.4 (t), 59.7 (t), 56.1 (t), 52.3 (d), 45.4 (q), 40.4 (d) (d, J_{CF} = 13 Hz), 8.5 (t) (d, J_{CF} = 8 Hz), 8.3 (t) (d, J_{CF} = 8 Hz); ir (neat) cm^{-1}: 1719, 1625, 1520, 1456, 1325; hrms (FAB): calcd for $C_{25}H_{24}F_2N_4O_5$ [M + H]$^+$: 499.1793; found: 499.1805.

1-Cyclopropyl-6,8-difluoro-7-(4-(R)-amino-2-methylpyrazolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (1, U-83140A).

A solution of quinolone **15** (112 mg, 0.225 mmol), in 4M aqueous hydrochloric acid (3 ml) and methanol (1 ml) was heated at reflux temperature for 4 h. The mixture was cooled to room temperature and stirred overnight. Next morning the mixture was again heated at reflux temperature for an additional 7 h, then it was cooled and concentrated *in vacuo*. The residue was triturated with 1:1:2/methanol:ethyl acetate:ether which resulted in the precipitation of the final product. The precipitated solid was filtered, washed with 1:1/ethyl acetate:ether, and dried to obtain pure quinolone U-83,140A (79 mg,

88%); mp >250°C (decomp.); ^{1}H nmr (CD_3OD) δ: 8.83 (s, 1H), 7.93 (d, J = 10.9 Hz, 1H), 4.50-4.39 (m, 1H), 4.32 (dd, J = 11.4, 7.6 Hz, 1H), 4.23-4.09 (m, 1H), 3.85-4.68 (m, 2H), 3.42 (dd, J = 12.3, 5.8 Hz, 1H), 2.82 (s, 3H), 1.40-1.16 (m, 4H); ir (neat) cm^{-1}: 3395, 1711, 1621, 1552, 1468, 1331; hrms (FAB): calcd for free base $C_{17}H_{18}F_2N_4O_3$ [m + H] + : 365.1425; found: 365.1447.

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