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β-Lactams from Ester Enolates and *N*-TMSimines: Enantioselective Synthesis of (*6R*, *7S*)-1β-3-Dimethyl-3-Isocephem.

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Abstract: Enantioselective synthesis of active isocephem **1** was accomplished employing as key-step the cycloaddition reaction of *N*-trimethylsilylimine of *O*-protected lactic aldehyde (**4**) and cyclic silyl derivative of glycine (**2**). The elaboration of hydroxyethyl side chain was carried out by functional group interchange (FGI) of the hydroxyl group by a thioacetoxy group, and finally six-membered ring assembly followed by attachment of necessary appendage to *N*-7 nitrogen atom.

Introduction

While the last few years have witnessed the studies on the preparation of literally thousand of semisynthetic penicillins[1] and cephalosporins[2], obtained by manipulation of the C-6, C-7, or C-3 side chains, it is only recently that β-lactam antibiotics, completely modified in the nucleus, as penems[3a], carbapenems[3b] and monobactams[3c], have been objects of intense research by the industrial and academic world. Whatever natural or synthetic in origin, this new generation of β-lactam antibiotics have shattered many of the notions regarding the requirements for optimal pharmacological activity[4].

During our recent work on chiral *N*-trimethylsilylimines, we disclosed the asymmetric synthesis of 3,4 disubstituted 2-azetidinones[5] based on the use of (*S*) lactic aldehyde as chiral auxiliary in the ester enolate-chiral imine route. This strategy is an efficient and versatile approach to the synthesis of carbapenem PS-5, PS-6 and monobactams. Along this line, we sought to apply our method to the synthesis of 4-(1-thioacetoxyethyl) azetidin-2-one and we describe herein the resulting route to novel *trans* 1β-methyl-3-methyl-isocephem[6] **1**.

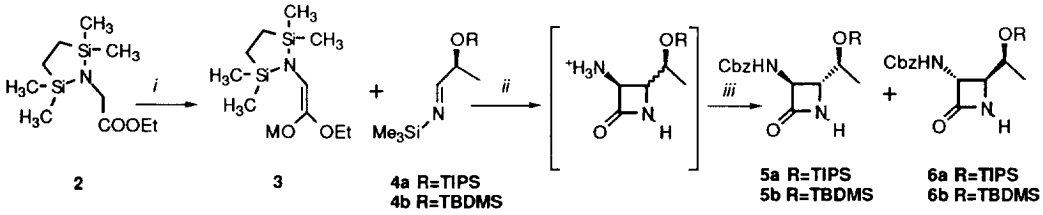
Results and Discussion

In our previous work we have demonstrated that the condensation reaction of *N*-trimethylsilylimine of (*S*)-lactic aldehyde, protected on the hydroxy functionality as *tert*-butyldimethylsilyl ether, with lithium ester enolate, drives, in high diastereomeric excess, to the azetidinone showing a *syn* relation-ship between the C-4 and C-4' substituents and a *trans* configuration between the C-3 and C-4 substituents on the azetidinone ring. This stereochemistry has been explained in terms of chelated controlled transition state[7] (Scheme 1). Unfortunately, whereas this stereochemical outcome allows the preparation of naturally occurring carbapenems, bearing in position 3 of the azetidinone ring an alkyl side chain with the natural (*3R*) configuration, it doesn't permit the preparation of natural (*3S*) amino azetidinones unless the unnatural (*R*)

lactic aldehyde is used; neverthless we have demonstrated that, to some extent, the judicious choice of cations present in the reactants allows the formation of (*3S*) amino azetidinone, starting from (*S*) lactic aldehyde, in satisfactory diastereomeric excess[5e]. Now we have found that the use of more sterically demanding *O*-protecting groups as triisopropylsilyl group (TIPS), simultaneous to that of non-chelating cations like sodium, increases the diastereomeric excess in the desired isomer[8]. (Scheme 1 and Table 1).

Our strategic plan starts from the readily available sodium enolate of ethyl-(2,2,5,5-tetramethyl-2,5-disilolidin)-1-acetate (STABASE)[9] **2** which upon treatment with one equivalent of *O*-triisopropylsilyloxy-*N*-trimethylsilylimine of (*S*) lactic aldehyde[5d] , obtained from (*S*)*O*-triisopropylsilyloxy- lactic aldehyde and lithium hexamethyldisilylamide (LiHMDSA), gives rise to azetidinones **5a** and **6a** in 60% chemical yields and 85/15 diastereomeric ratio. These compounds have been isolated as carbobenzyloxy derivatives through removal of disilylcyclopentane ring by acid-catalyzed hydrolysis[9] and protection of the resulting amino group by carbobenzoxychloride.[10] The use of lithium enolate of STABASE increases the chemical yields and the diastereomeric excess but of the undesired diastereoisomer. (Table 1).

Scheme 1



i : $MN(SiMe_3)_2$, THF, -78°C. *ii* : THF, -78°C, then r.t. 8 hrs; HCl 1N (pH 3), 1h; *iii:* Acetone, $NaHCO_3$ (pH 8), CbzCl, 3hrs.

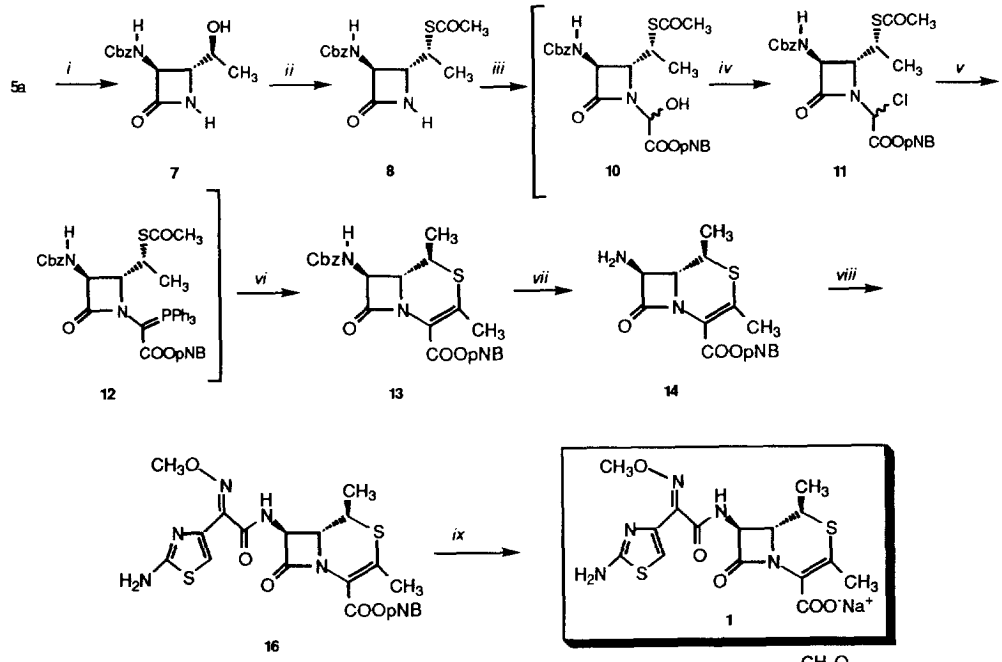
Table 1: Condensation of enolate **3** and imine **4**

Entry	M	R	Ratio **5/6**
1	Li	TIPS	10/90
2	Li	TBDMS	2/98
3	Na	TIPS	85/15
4	Na	TBDMS	60/40

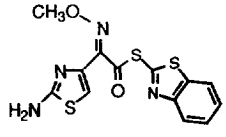
The so prepared azetidin-2-one **5a,** possessing the correct stereochemistry on the C-4 and C-4' stereocenters, after deprotection of the TIPS group (hydrogen fluoride in acetonitrile[11]), was converted, following the Mitsunobu procedure[12] (diisopropylazodicarboxylate (DIAD), Ph_3P, CH_3COSH in THF), to tioester **8.** *N*-Acylation[13] of **8** with p-nitrobenzyl glyoxylate ethylhemiacetal **9** (pNBOOCCH(OH)OEt/ Benzene/ Molecular Sieves) gave the adduct **10** which, in turn, was converted, by treatment with thionyl chloride in dioxane in the presence of Hunig's base, to the corresponding chloride **11**. The crude reaction mixture was treated with PPh_3 to give the phosphorane **12,** which upon reflux in boiling toluene gave the bicyclic derivative **13** (Scheme 2). Anisole/$AlCl_3$ mediated deblocking of the carbobenzoxy group[14] followed by acylation[15] of the free amino group with (2-aminothiazol-4-yl)-methoxyimino-thioacetic acid S-

benzothiazol-2-yl-ester (MAEM) **15** , provided the bicyclic intermediate **16** which was finally converted to the target compound **1** by hydrogenolysis (Scheme 2).

Scheme 2



i : HF_{aq}, 5% in CH_3CN; *ii* : DIAD, PPh_3, CH_3COSH, THF, r.t.; *iii* : OEt(OH)CHCOOpNB(**9**) , Molecular sieves 4 Å, Bz; *iv* : Polymeric Hunig base, $SOCl_2$, Dioxane; *v*: Polimeric Hunig base, PPh_3, Dioxane; *vi* : Toluene, reflux; *vii*: $AlCl_3$, Anisole; *iii* : TEA,/ EtOAc; *ix* : H_2, Pd/C 10%, $NaHCO_{3\,aq}$.



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In vitro Biological Evaluation

The minimum inhibitory concentration (MICs: μg/ml) against test organisms were determined by an agar dilution method. The in vitro activities of **1** are summarized in Table 2. The antibacterial activities of Cefachlor as reference compound are also presented.

Table 2: "*In vitro*" Antibacterial Spectra of **1**

Bacteria	MIC (μg/ml)	Cefachlor
Staphilococcus aureus (Benzylpenicillin-susceptible)	2.0	0.5
Staphilococcus aureus (Penicillinase-producing)	2.0	2.0
Streptococcus pyogenes	0.5	0.25
Streptococcus pneumoniae	4.0	2.0
Haemophilus influenzae	4.0	4.0
Escherichia coli	2.0	1.0
Klebsiella pneumoniae	4.0	<0.5
Proteus mirabilis	4.0	1.0
Salmonella tiphi	32.0	<0.5
Shigella floxneri	8.0	2.0
Pseudomonas aeruginosa	>128.0	32.0

EXPERIMENTAL SECTION

General. For purification of crude reaction mixtures, flash chromatography using silica gel 70-230 mesh was used. Analytical thin layer chromatography was performed by using precoated silica gel F-254 plates; products were observed by using ultraviolet light, iodine or phosphomolybdate spot tests. THF and diethyl ether were predried over CaH_2 and distilled from sodium benzophenone under an argon atmosphere prior to use. The composition of the eluting solution is given in brackets. Acetone was distilled over $KMnO_4$. NMR data were obtained as $CDCl_3$ solution, unless otherwise stated, on VXR 200 spectrometer, chemical shifts are reported in parts per million (ppm) from internal tetramethylsilane, and coupling constants (J) are reported in Hertz. IR spectra were obtained as chloroform solutions, unless otherwise stated, and are reported in cm^{-1}. Optical rotations were taken at 25 °C. HPLC analyses were performed on RP 18 column (250x4.6 mm, Sperex 5, 2.00ml/min, 10%CH_3CN+10%H_20 (solvent A) 90% H_20 (Solvent B). Melting points are uncorrected. Mass spectra were recorded at an ionization energy of 70 eV.

(*S*)-2-[(triisopropylsilyl)oxy]-*N*-(trimethylsilyl)propanimine. 4a

To a 1 M solution of LiHMDS in THF (33.7 ml) were added, at -40°C, 7.0 g (33.7 mmol) of (*S*)-2-(triisopropylsilyloxy)-propanal[16] in 30 ml of THF. The mixture was stirred at -40°C for 40 min and the resulting cold solution of *N*-(trimethylsilyl)imine **4a** was used directly in the following reaction. IR (THF) 1680.

(*1'S, 3S, 4S*)- and (*1'S, 3R, 4R*)-3-Benzyloxycarbonyl-Amino-4-(1-triisopropylsilyloxyethyl) Azetidin-2-ones 5a and 6a.

To a 1 M solution of NaHMDS in THF (33.7 ml) were added, a -78°C, 8.3 g (33.7 mmol) of STABASE **2** in 10 ml of THF. The mixture was stirred for 2 h followed by addition of *N*-(trimethylsilyl)imine **4a** *via* cannula over a 10 min period. The mixture was allowed to warm, spontaneously, to room temperature and stirred overnight. To this brown solution, at 0°C, 50 ml of NH_4Cl_{aq} were added and the pH was adjusted to 4 by addition of 1 N solution of HCl, followed by addition of 5.0 g of $NaHCO_3$ (pH 8). Benzylchloroformate (6.8 g, 40 mmol), dissolved in 20 ml of acetone, was added dropwise. After stirring at room temperature (3 hrs), the reaction mixture was extracted with ethyl acetate (500 ml) and the organic layers were washed with brine, dried and concentrated in vacuo. The residue was purified by flash chromatography (hexane-ethyl acetate 1:1) to give 6.5 g of the β-lactam **5a** and 1.2 g of the β-lactam **6a** in 85/15 ratio and 60% overall yield. **5a:** mp 37°C; $[\alpha]^{25}_D$=-8.7 (*c* 3.034, $CHCl_3$); IR ($CHCl_3$) 3427, 1772, 1724; ^1H NMR 1.05 (s, 18H), 1.23 (d, 3H, J=6.3), 3.58 (m, 1H), 4.15 (m, 1H), 4.70 (dd, 1H, J_1=2.1, J_2=8.6), 5.10 (s, 2H), 5.8 (d, 1H, J=8.6), 6.40 (bs, NH), 7.33 (s, 5H); ^{13}C NMR 167.7, 155.5, 136.0, 128.5, 128.2, 128.1, 67.0, 66.9, 62.5, 58.7, 19.9, 18.0, 12.4; **6a**: $[\alpha]^{25}_D$=+22.37 (*c* 1.600, $CHCl_3$); ^1H NMR 1.05 (s, 18 H), 1.2 (d, J=6Hz, 3H), 3.48 (dd, J_1=2.2, J_2=6.5 1H), 4.00 (m, 1H), 5.00 (quintet, 1H, J=6.5), 4.47 (dd, 1H, J_1=2.1 J_2= 8.2), 5.10 (s, 2H), 5.95 (d, 1H, J=8.2), 6.55 (s, NH), 7.30 (s, 5H); ^{13}C NMR 168.6, 155.8, 136.2, 128.5, 69.90, 67.0, 63.6, 60.3, 20.10, 18.1, 12.5.

(*1'S, 3S, 4S*)-3-Benzyloxycarbonyl-Amino-4-(1-Hydroxyethyl)Azetidin-2-one. 7

The β-lactam **5a** (4.6 g, 11 mmol) dissolved in 100 ml of acetonitrile containing 5 ml of a 40% solution of HF_{aq}.was stirred at r.t. and the reaction was monitored by t.l.c. eluting with hexane-ethyl acetate 50:50. When the reaction was complete, pH 7 was reached by addition of $NaHCO_{3aq}$. The mixture was extracted with ethyl acetate (200 ml); the organic layers were washed with brine, dried and concentrated in vacuo to give **7** as a white solid (2.8 g, 97%). mp 177°C; $[\alpha]^{25}_D$=-37.2° (*c* 1.586, CH_3OH); IR (nujol) 3330, 3210, 1775, 1730, 1697; ^1H NMR (acetone D_6) 1.14 (d, 3H, J=6.3), , 3.46 (dd, 1H, J_1=2.4, J_2=4.6), 3.84 (m, 1H), 4.3 (d, J=4, OH), 4.62 (dd, 1H, J=2.44, 8.6), 5.10 (s, 2H), 7.37 (m, 7H, 5 Ar and 2 NH); ^{13}C NMR (acetone D_6) 167.5, 156.2, 138.0, 129.2, 128.7, 128.6, 67.1, 66.9, 62.5, 60.7, 19.9; MS m/z 221 (M^+ -43).

(*1'R, 3S, 4S*)-3-Benzyloxycarbonyl-Amino-4-(1-Acetylthioethyl)Azetidin-2-one. 8

Diisopropyl azodicarboxylate (0.15 g, 0.76 mmol) was added to a solution of Ph_3P (0.2 g, 0.76 mmol) in 2 ml of THF at 0°C. A white precipitate was obtained; the mixture was stirred for 30 min then a solution of alcohol **7** (0.1 g, 0.38 mmol) and thiolacetic acid (0.057 g, 0.76 mmol) in 5 ml of THF was added dropwise over 5 min period. The mixture was stirred for 1 h at 0°C and then at room temperature for 1 h. A clear yellow solution resulted. The solution was concentrated in vacuo and the residue was purified by flash-chromatography (hexane-ethyl acetate 40:60) to give 86 mg of thioester 8 as an oil (72% yield). $[\alpha]^{25}_D$=+19.8° (*c* 1.262, $CHCl_3$); IR ($CHCl_3$) 3400, 1777, 1724, 1695; ^1H NMR 1.38 (d, 3H, J=6), 2.33 (s, 3H), 3.70 (m, 2H), 4.46 (dd, 1H, J_1=0.4, J_2=8.0), 5.11 (s, 2H), 5.70 (d, 1H, J=8.0), 6.38 (bs, NH), 7.34 (s, 5H); ^{13}C NMR 195.0, 166.9, 155.7, 136.1 , 128.7, 128.4, 128.3, 67.4, 62.5, 61.3, 41.7, 30.9, 17.6; MS m/z 204 (M^+-118).

(*6R, 7S*)-7-Benzyloxycarbonylamino-1β,3-dimethyl-3-isocephem-4-Carboxylic acid p-Nitrobenzyl ester. 13

The tioester **8** (0.3 g, 0.93 mmol) and *p*-nitrobenzylglyoxylate ethyl hemiacetal (0.6 g, 2.3 mmol) were dissolved in 15 ml of benzene and activated molecular sieves were added . The mixture was refluxed for 24 hrs. The reaction was monitored by t.l.c. (ethyl acetate-toluene 70:30). The solvent was evaporated in vacuo and the crude epimeric mixture **10** was used in the next step. IR ($CHCl_3$) 3450, 1771, 1721. Polymeric Hunig base (1.5 g, 2.3 mmol) was stirred for 30 min with 5 ml of dioxane. A solution of hemiaminals **10** (0.4 g, 0.75 mmol) in 5 ml of dioxane was added in one pot at room temperature followed by the dropwise addition of a solution of thionyl chloride (0.27 g, 2.3 mmol) in 5 ml of dioxane. The mixture was stirred for 3 h; the polymeric base was filtered off and the solvent was evaporated in vacuo to give a syrupy epimeric mixture of chlorides **11**. IR ($CHCl_3$) 3450, 1787, 1762, 1724, 1700. To a suspension of polymeric Hunig base (0.66 g, 1mmol) in 3 ml of dioxane, after stirring for 30 min, were added the epimeric mixture **11** (0.4 g, 0.73 mmol) in 10 ml of dioxane and triphenylphosphine (0.29 g, 1.1 mmol). The mixture was heated at 70°C for 3 days. After the disappearance of starting materials (t.l.c. hexane-ethyl acetate 60:40) the polymeric base was filtered off and the solvent was evaporated in vacuo to give the phosphorane **12** . IR ($CHCl_3$) 3550, 1770, 1722, 1686. The crude reaction mixture (0.26 g, 0.33 mmol) was dissolved in 100 ml of toluene containing traces of hydroquinone and the mixture was refluxed for 5 days. The solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2-ethyl acetate 75:25) to give **13** (135 mg, 30% overall yield). $[\alpha]^{25}_D$=+9.4° (*c* 0.868, $CHCl_3$); IR ($CHCl_3$) 3550, 1770, 1720 ; ^1H NMR 1.46 (d, 3H, J=6.2), 2.20 (s, 3H), 3.14 (m, 1H), 3.21 (dd, 1H, J_1=0.4, J_2=9.1), 4.40 (dd, 1H, J_1=0.4, J_2=7.4), 5.13 (AB, 2H), 5.33 (s, 2H), 5.70 (d, 1H, J=7.4), 7.35 (s, 5H), 7.61 (d, 2H), 8.19 (d, 2H); ^{13}C NMR 160.9, 160.6, 155.5, 147.7, 142.8, 135.7, 128.8, 128.6, 128.5, 128.2, 123.7, 117.0, 116.1, 67.5, 65.9, 63.8, 58.7, 39.4, 19.4, 15.5; MSm/z 317 (M^+-180).

(*6R, 7S*)-7-amino-1β,3-dimethyl-3-isocephem-4-Carboxylic acid p-Nitrobenzyl ester. 14

To a solution of **13** (0.1 g, 0.2 mmol) in 2 ml of anisole was added anhydrous aluminium chloride (40 mg, 0.3 mmol) at room temperature. The reaction was monitored by t.l.c. (CH_2Cl_2 : ethyl acetate 75:25). The crude mixture was filtered and the solvent was evaporated. The residue was purified by flash chromatography to give **14** (47 mg, 65%). $[\alpha]^{25}_D$=-48.6° (*c* 0.596, $CHCl_3$); IR ($CHCl_3$) 3630, 1760, 1715; ^1H NMR 1.43 (d, 3H, J=6), 2.20 (s, 3H), 2.51 (bs, NH_2), 3.10 (m, 2H), 3.80 (d, 1H, J=0.4), 5.34 (s, 2H), 7.63 (d, 2H), 8.22 (d, 2H); ^{13}C NMR 165.2, 160.8, 147.7, 142.9, 134.3, 128.9, 123.7, 117.2, 66.6, 65.8, 59.9, 39.6, 19.3, 15.6; MS m/z 363.

(*6R, 7S*)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-1β,3-dimethyl-3-isocephem-4-Carboxylic acid p-Nitrobenzyl ester . 16

To a solution of **14** (60 mg, 0.16 mmol) in 6 ml of anhydrous ethyl acetate was added triethylamine (46 mg, 0.30 mmol) and MAEM **15** (59 mg, 0.16 mmol) and the slurry was stirred at room temperature for 1 h. The mixture was concentrated in vacuo and the residue was purified by flash chromatography (ethyl acetate) to give **16** (69 mg, 76%). $[\alpha]^{25}_D$=-93° (*c* 1.640, $CHCl_3$); 3690, 3627, 3450, 1764, 1721, 1680, 1545 ; ^1H NMR 1.52 (d, 3H, J=6), 2.25 (s, 3H), 3.27 (m, 2H), 3.94 (s, 3H), 4.87 (dd, 1H, J_1=1.2, J_2=7.6), 5.33 (AB, 2H), 5.62 (bs, NH_2), 6.68 (s, 1H), 7.53 (d, 2H), 8.02 (d, 2H), 8.94 (d, NH); ^{13}C NMR 168.4, 162.4, 161.5, 160.7, 156.8, 147.8, 147.4, 142.7, 136.4, 128.6, 123.8, 117.1, 111.6, 65.9, 63.1, 61.7, 59.0, 39.8, 19.6, 15.8.

(*6R, 7S*)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-1β,3-dimethyl-3-isocephem-4-Carboxylic acid Sodium Salt. 1

A solution of *p* -nitrobenzyl ester **16** (30 mg, 0.055 mmol) in 5 ml of THF containing a catalytic amount of 10% Pd/C and 4.6 mg (0.055 mmol) of $NaHCO_3$ in 3 ml of H_20 was hydrogenated on a Parr shaker at room temperature (40 psi, 1 h). The catalyst was filtered through Celite and the filtrate was washed with ether. Filtration through XAD4 resin, eluting with water, followed by freeze-drying of the fraction containing the target, gave **1** as a white solid (7 mg, 30%). $[\alpha]^{25}_D$=-54° (*c* 0.740, H_2O); IR (nujol) 3600-3100, 1744. UV λ_{max} 286, 235 in H_2O; ^1H NMR (D_2O) 1.24 (d, 3H, J=6.5), 1.83 (s, 3H), 3.20 (m, 1H), 3.30 (dd, 1H, J_1=1.9, J_2=9.2), 3.81 (s, 3H), 4.70 (d, 1H, J=1.9), 6.78 (s, 1H); ^{13}C NMR 171.0, 168.9, 164.3, 162.3, 147.9, 140.3, 123.0, 120.9, 113.2, 62.7, 59.7, 58.4, 37.3, 17.5, 14.5.

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