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A facile synthesis of the spiroindoline-based growth hormone secretagogue, MK-677

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Abstract

A facile and improved route for the synthesis of the orally active spiroindoline-based growth hormone secretagogue, MK-677 was described. The key step adopted the Fischer indole/reduction strategy. The preparation of the key intermediates *N*-protected piperidine carboxaldehyde **5** and the *N*-Boc-*O*-benzyl-D-serine (**2**) are also optimized.

Keywords: MK-677; Synthesis; Improved route; Fischer indole/reduction

MK-677 is a medicine which acts as a potent, orally active growth hormone secretagogue, mimicking the growth hormone stimulating action of the endogenous hormone ghrelin. It has been demonstrated to increase the release of, and produces sustained increases in plasma levels of several hormones including growth hormone and IGF-1, however, without affecting cortisol levels. It is currently under development as a potential treatment for reduced levels of these hormones, such as in growth hormone deficient children or elderly adults, and human studies have shown it to increase both muscle mass and bone mineral density, making it a promising therapy for the treatment of frailty in the elderly. It also alters metabolism of body fat and so may have application in the treatment of obesity. A survey of the literature revealed only two reports on the total synthesis of MK-677, which were all accomplished by Merck research laboratories in 1997 and 1998 [1]. However, there were some drawbacks such as some toxic agents $(COCl)_2$ and high pressure were required in the earlier research work. Hence, the profound clinical use encouraged us to seek a facile process and more environmentally friendly way to accomplish the total synthesis of MK-677. Here, an improved synthesis procedure for the preparation of MK-677 was described.

Retrosynthetic analysis of the MK-677 was described in Fig. 1. MK-677 could be derived from spiroindoline **1** *via* double amidations with protected amino acids **2** and **3** respectively. Spiroindoline **1** was expected from phenylhydrazine **4** and *N*-protected piperidine carboxaldehyde **5** using Fischer indole type approach [2]. In turn, the aldehyde **5** could be easily prepared from commercially available isonipecotic acid (**6**) *via* three steps.

The preparation of the aldehyde **5** was begun with isonipecotic acid (**6**) (Scheme 1). Thus, reduction of acid **6** with $LiAlH_4$ gave the amino alcohol **7**, followed by protection of the secondary amino group with CbzCl in the presence of

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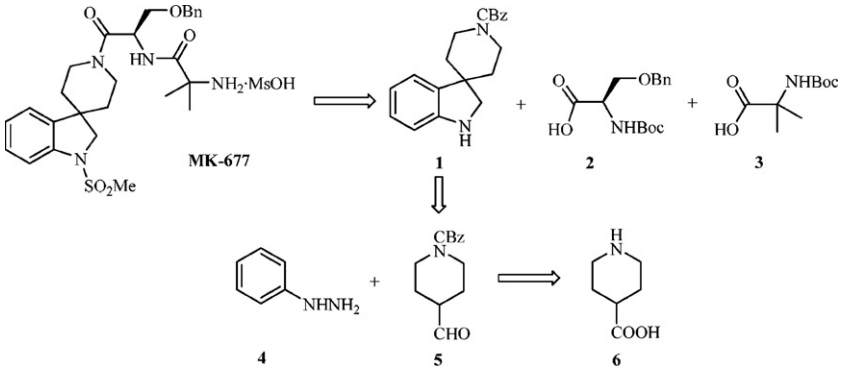
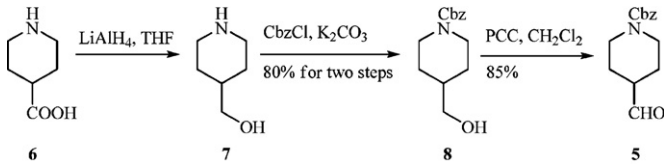


Fig. 1. Retrosynthetic analysis of MK-677.

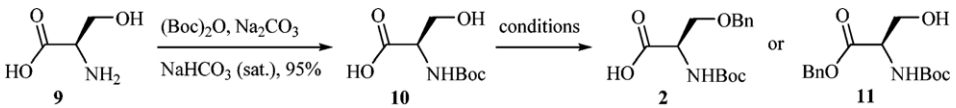


Scheme 1. The preparation of *N*-protected piperidine carboxaldehyde **5**.

K_2CO_3 provided alcohol **8** in 80% yield for two steps [3]. Then, oxidation of **8** using PCC in CH_2Cl_2 provided aldehyde **5** in 85% yield. All reactions were carried out at room temperature and ordinary pressure, which avoided the using of $(COCl)_2$ and high pressure reported previously [1], and guaranteed a totally convenient process for the preparation of the key intermediate **5** by directly reduction of the acid.

The preparation of another key intermediate, *N*-Boc-*O*-benzyl-D-serine (**2**) was started from known D-serine **9** (Scheme 2). Thus, protection of the amine group in **9** by *tert*-butyl dicarbonate [$(Boc)_2O$] in the presence of Na_2CO_3 in saturated $NaHCO_3$ aqueous afforded the amino acid **10** in 95% yield [4]. However, the consecutive selective protection of the primary alcohol in **10** without esterification was a challenge to us. To enhance the reactive efficiency of the amidation step between compounds **13** and **2**, the acid **10** must be converted completely. Initially, common conditions (NaH, BnBr, DMF) was adopted for the protection of the primary alcohol in **10**, however, there was nearly a half of starting material converted with the low yield of **2** (Table 1, entry 1) [5,6]. Then, the same reaction was carried out at 0 °C and extended the reaction time to 48 h, the yield of the desired product had a slightly increase (entry 2). But the conversion of the compound **10** decreased when the temperature enhanced to 40 °C (entry 3). Further screening of the reaction conditions using the catalysts $(n\text{-}C_4H_9)_4NI$ or KI [6] did not enhance the yield of the compound **2** (entry 4). Changing the reaction solvent or treatment with Ag_2O, only the ester **11** was obtained (entry 5 and 6) [7,8]. According to literature precedent, Wang tried the same reaction and achieved similar results at room temperature [9]. When the reaction ran with NaO*t*-Am as base at −10 °C, the yield was improved to 74% [1], and 45% with Na/NH_3 (l) at −50 °C to −30 °C [10]. So in our case, the reaction was carried out in DMF at −40 °C for 5 h to provide the desired amino acid **2** in 75% yield (entry 7). It is due to the intramolecular hydrogen bond between the NH and CO_2H stabilized at low temperature, which made the S_N2 process occurred in the hydrooxyl group.

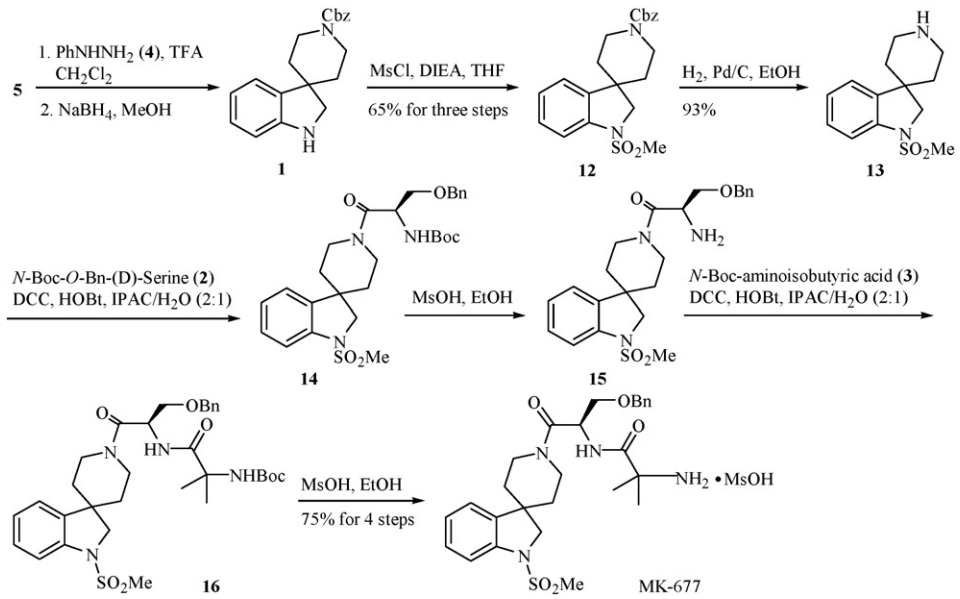
With the key intermediates **5** and **2** in hand, we first investigated the formation of spiroindoline unit using Fischer indole/reduction strategy (Scheme 3). Hence, treatment of an equivmolar mixture of aldehyde **5** and phenylhydrazine **4** with 2.5 equiv of TFA in CH_2C1_2 at 35 °C for 16 h gave a nearly quantitative yield of imine with no evidence of the



Scheme 2. The preparation of **2**.

Table 1
The optimization of selective protection of primary alcohol in **10**.

Entry	Conditions	Time (h)	Products	Yield (%)
1	NaH, BnBr, DMF, rt	24	**2**, **10** (1:1)	37 for **2**
2	NaH, BnBr, DMF, 0 °C	24–48	**2**, **10** (3:2)	46 for **2**
3	NaH, BnBr, DMF, 40 °C	24	**2**, **10** (1:3)	18 for **2**
4	NaH, BnBr, $(n\text{-}C_4H_9)_4NI$ or KI, DMF, 40 °C	24	**2**, **10** (1:3)	18 for **2**
5	NaH, BnBr, DMF/THF, rt	24	**11**	65
6	Ag_2O, BnBr, THF, rt	24	**11**	65
7	NaH, BnBr, DMF, −40 °C	5	**2**	75



Scheme 3. Synthesis of MK-677.

Wagner-Meerwein ring expansion product [11]. *In situ* reduction of the imine with $NaBH_4$ in MeOH gave spiroindoline **1**. Subsequently, sulfonamidation of **1** with MsCl and DIEA in THF provided the sulfonamide **12** in 65% yield for three steps from aldehyde **5**. Soon afterward catalytic hydrogenolysis of **12** using 10% Pd/C in EtOH under normal pressure of H_2 atmosphere afforded the deprotected piperidine **13** in 93% yield (high pressure was used in the literature [1]). Spiroindoline **13** was amidated with *N*-Boc-*O*-benzyl-D-serine (**2**) in the presence of DCC and 1-hydroxybenzotriazole (HOBt) in 2:1 isopropyl acetate (IPAC)-water to give the *N*-Boc-monopeptide **14**, followed by deprotection with MsOH in EtOH to provide compound **15**. Then the second amidation with *N*-Boc-amino-isobutyric acid (**3**), followed by Boc-deprotection of the resulting compound **16** gave MK-677 in 75% yield from **13** without isolation of any intermediates. Crystallization of crude MK-677 as the MsOH salt from EtOAc-EtOH gave the pure drug substance. The NMR data of synthesized MK-677 were identical with the reported data [12].

In conclusion, an improved synthesis of *N*-protected piperidine carboxaldehyde **5** and an optimization of preparation conditions for *N*-Boc-*O*-benzyl-D-serine (**2**) were explored. Thus a facile process for the synthesis of the Growth Hormone MK-677 from commercially available starting material had also been accomplished.

Acknowledgments

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[7] Data of compound **2** [5b]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.1 (s, 1H, COOH), 7.31–7.27 (m, 5H, 5 × ArH), 5.52 (d, 1H, J = 7.6 Hz, NH), 4.51–4.48 (m, 3H, $ArCH_2$ and H-2), 3.92–3.89 (m, 1H, H-3a), 3.72–3.69 (m, 1H, H-3b), 1.44 (s, 9H, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7 (CO), 155.6 (CO, C-1), 137.3 (C), 128.3 (CH), 127.7 (CH), 127.5 (CH), 80.2 (C), 73.2 (CH_2), 69.7 (CH_2, C-3), 53.7 (CH, C-2), 28.2 (3 × CH_3); IR (KBr, ν_{max}/cm^{-1}): 3438, 2979, 2624, 1719, 1505, 1367, 1164, 738 cm^{-1}; EIMS (*m*/*z*, %): 295 (M^+, < 1), 239 (2), 194 (3), 148 (13), 132 (6), 133 (5), 91 (100), 57 (49).

[8] Data of compound **11** [6]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 5H, 5 × ArH), 5.73 (d, 1H, J = 8.0 Hz, NH), 5.17 (d, 2H, J = 1.6 Hz, $ArCH_2$), 4.39 (s, 1H, CH, H-2), 3.98–3.94 (m, 1H, H-3a), 3.86–3.83 (m, 1H, H-3b), 3.45 (s, 1H, OH), 1.42 (s, 9H, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (CO), 155.7 (CO, C-1), 135.2 (C), 128.4 (CH), 128.2 (CH), 127.9 (CH), 80.0 (C), 67.0 (CH_2), 62.9 (CH_2, C-3), 55.7 (CH, C-2), 28.1 (3 × CH_3); IR (KBr, ν_{max}/cm^{-1}): 3365, 2979, 1693, 1520, 1369, 1165, 1062, 783 cm^{-1}; EIMS (*m*/*z*, %): 295 (M^+, <1), 239 (3), 194 (8), 148 (30), 132 (13), 133 (11), 91 (100), 57 (49).

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[12] Data of synthesized MK-677: in the literature, some of ^{1}H NMR and ^{13}C NMR signals appeared as pairs of peaks due to the presence of amide rotamers. Here, the ^{1}H and ^{13}C NMR data of the two rotamers were also described. ^{1}H NMR (400 MHz, CD_3OD): δ 7.38–7.22 (m, 12H), 7.22–7.18 (m, 3H), 7.06 (t, 1H, J = 7.2 Hz), 6.99 (t, 1H, J = 7.6 Hz), 6.80 (d, 1H, J = 7.6 Hz), 5.27–5.13 (m, 2H), 4.58–4.46 (m, 6H), 4.09–3.98 (m, 2H), 3.93 (s, 4H), 3.87–3.74 (m, 4H), 3.26–3.17 (m, 2H), 2.97 (s, 3H), 2.95 (s, 3H), 2.89–2.80 (m, 2H), 2.73 (s, 6H), 1.98–1.92 (m, 1H), 1.87–1.65 (m, 5H), 1.65 (s, 5H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD): δ 173.1 (173.0, CO), 170.2 (170.0, CO), 142.7 (142.6, C), 139.6 (139.4, C), 139.3 (C), 129.9 (129.8, CH), 129.7 (129.6, CH), 129.2 (CH), 129.13 (129.07, CH), 125.0 (CH), 124.6 (CH), 114.5 (114.4, CH), 74.5 (74.3, CH_2), 71.0 (70.2, CH_2), 60.3 (60.0, CH_2), 58.5 (C), 58.4 (CH_2), 51.6 (50.9, CH), 44.5 (44.4, CH_2), 44.2 (C), 41.1 (40.8, CH_2), 39.7 (CH_3), 37.6 (36.9, CH_2), 34.7 (CH_3), 24.4 (24.3, CH_3), 24.2 (24.1, CH_3).