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A Convenient Method for the Asymmetric Synthesis of KAD-1229

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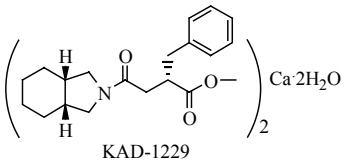
Abstract: A new method for preparation of the potent hypoglycemic KAD-1229 was developed. The key step of this method is diasteroselective alkylation in high optical purity and good yield by using easily available Oppolzer's camphor sultam as chiral auxiliary.

Keywords: KAD-1229, mitiglinide, camphorsultam.

KAD-1229 (**Figure 1**) is a novel hypoglycemic agent with a chemical structure different from that of the sulfonylureas which has a rapid-onset but short-lasting hypoglycemic effect. KAD-1229 inhibits the ATP-sensitive potassium channels in pancreatic β-cell and stimulates insulin release like sulfonylureas[1]. The stereochemistry is very important for the activity of the compound and (*S*)-absolute configuration is necessary for insulin secretory effect. Recently, KAD-1229 has been in phase III clinical trials in Japan and in phase II clinical trials in Europe and the U.S.A. for the treatment of type 2 diabetes, expected to be launched in near future. The compound KAD-1229 has been obtained by several related methods involving optical resolution[2], asymmetric synthesis using Evan's chiral enolate methodology[3] and asymmetric hydrogenation with the chiral diphosphine complex of rhodium or ruthenium[4]. We herein report a facile and more efficient asymmetric synthetic strategy for its large scale preparation.

We considered Oppolzer's camphor sultam serve as efficient, versatile and practical chiral auxiliaries. It is easy to prepare from inexpensive camphor. Highly π-face-selective alkylations of enolates followed by nondestructive removal of the auxiliary afforded a highly optically active carboxylic acid and absolute configuration of the product was easily detected. The operation is very facile and simple, and products

Figure 1



KAD-1229

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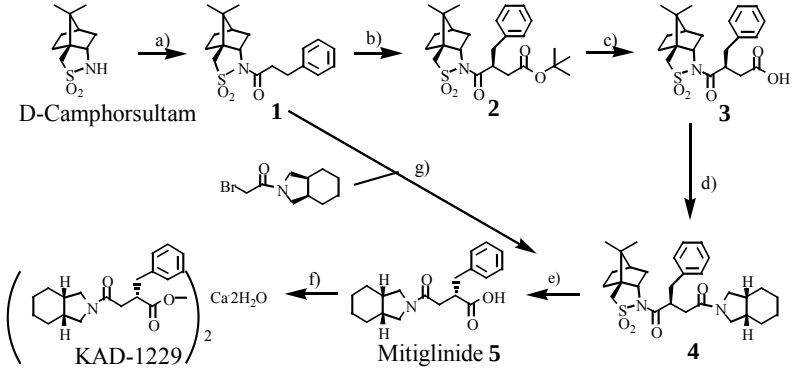
Scheme 1



a) 3-phenylpropionyl chloride, NaH, Tol., r.t., 91% or CH_3CN, refluxing, 10 h, 89%; b) NaHMDS, *tert*-butyl bromoacetate, HMPA, THF, -78~0℃, 16 h, 92%; c) TFA, CH_2Cl_2, 87%; d) NMM, $ClCO_2{}^iBu$, *cis*-hexahydroisoindole, CH_2Cl_2, 84%; e) LiOH, aqueous THF, 30% H_2O_2, 93%; f) 2mol/L NaOH, $CaCl_2$, H_2O/EtOH, 91%; g) NaHMDS, N-(bromoacetate)-*cis*-hexahydroisoindole, HMPA, THF -78~0℃, 16 h, 85%.

can be purified by crystallization. Recycling of the chiral auxiliary is practical. This method is suitable for a large scale manufacturing of pharmaceutical grade KAD-1229.

The process for the preparation of KAD-1229 (**Scheme 1**) starts from D-(-)-camphorsultam, which is readily available in 85% yield from the natural D-(+)-camphor[5]. Treatment D-(-)-camphorsultam with an excess of 3-phenylpropionyl chloride in the presence of NaH at room temperature gave **1** in 91% yield[6]; An alternative procedure was performed by refluxing D-(-)-camphorsultam with 3-phenylpropionyl chloride in CH_3CN[7], and the crude **1** was purified by recrystallization from EtOH/H_2O in 89% yield. Reaction of **1** with an equimolar amount base formed chiral enaolate in dry ice/ethanol bath, followed by alkylation with *tert*-butyl bromoacetate to give **2**[8]. The difference of organic base has large influence on the yield of **2**, such as the yield of reaction using *n*-BuLi, lithium diisopropylamine (LDA) or sodium hexamethyldisilazide (NaHMDS) was 30~40% 60%, 92% respectively. The ester **2** was cleaved by using TFA in dichloromethane to give **3** in 87% yield[9]. Acylation of *cis*-hexahydroisoindole with **3** using mixed anhydride method afforded **4** in 84% yield[10]. Compound **4** can be also obtained by direct alkylation of acylsultam with N-(bromoacetate)-*cis*-hexahydroisoindole in 85% yield. Nondestructive cleavage of **4** by hydroperoxide-assisted saponification regenerated sultam (96% recovered yield) and gave Mitiglinide **5** in 93% yield with >99% *ee* (determined by HPLC analysis of the corresponding methyl ester) [8]. The Mitiglinide **5** was treated with 2 mol/L sodium hydroxide, followed by treatment with calcium chloride, and recrystallization from aqueous ethanol to give KAD-1229 in 91% yield. The overall yield was 57%, the melting point and specific rotation data were identical with literature[2].

In conclusion, we have developed an efficient and practical asymmetric route for the preparation of KAD-1229, using Oppolzer's camphor sultam asymmetric alkylation as a key step.

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References and Notes

1. H. Ohnota, T. Koizumi, N. Tsutsumi, *et al.*, *Pharmacol. Exp. Ther.,* **1994**, *269*, 489; H. Ohnota, M. Kobayashi, T. Kiozumi, *et al.*, *Biochem. Pharmacol.,* **1995**, *49*, 165; M. Kinukawa, H. Ohnota, T. Azisawa, *Br. J. Pharmacol.,* **1996**, *117*, 17021.
2. T. Yamaguchi, T. Yanagi, H. Hokari, *et al.*, *Chem. Pharm. Bull.,* **1997**, *45*, 1518; T. Yamaguchi, T. Yanagi, H. Hokari, *et al.*, *Chem. Pharm. Bull.,* **1998**, *46*, 337.
3. D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.,* **1982**, *104*, 1737.
4. J. P. Lecouve, C. Fugier, J. C. Souvie, WO pat. 9901430, **2000**.
5. M. Vandewalle, J. Van der Eycken, W. Oppolzer, *et al.*, *Tetrahedron,* **1986**, *42*, 4035; F. A. Davis, J. C. Towson, M. C. Weismiller, *et al.*, *J. Am. Chem. Soc.,* **1988**, *110*, 8477.
6. D. Brundish, A. Bull, V. Donovan, *et al.*, *J. Med. Chem.,* **1999**, *42*, 4584.
7. M. C. William, B. Corey, *J. Org. Chem.,* **1998**, *63,* 6732.
8. W. Oppolzer, R. Moretti, S. Thomi, *Tetrahedron Lett.,* **1989**, *30*, 5603.
9. H. Heitsch, R. Henning, H. W. Kleemann, *et al.*, *J. Med. Chem.,* **1993**, *36*, 2788.
10. J. J. Plattner, P. A. Marcotte, H. D. Kleinert, *et al.*, *J. Med. Chem.,* **1988**, *31*, 2277.
11. All new compounds were characterized by ^{1}H-NMR, MS and element analysis. The key proced ures: To a solution 1.1 mol-equiv of **1** (1.74 g, 5.00 mmol) in THF (15 mL) at -78℃ under nitrogen was added NaHMDS (5.50 mL, 1 mol/L solution in THF) deopwise over 5 min, and the solution was stirred at -78℃ for 0.5 h. Then a solution of *tert*-butyl bromoacetate (2.20 mL, 15.00 mmol) and HMPA (2.62 mL, 15.00 mmol) in THF (5 mL) was added dropwise over 10 min. After stirring at -78℃ for 16 h, the solution was warmed to r.t. and stirred for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the reaction mixture was extracted with Et_2O to give crude **2** (*d.e.*>93%). Crystallization from methanol gave **2** as crystal (2.13 g, 92%). Hydroperoxide-assisted saponification: To a solution of **4** (1.64 g, 3.20 mmol) in THF/H_2O (25 mL, 4:1) were added 30% H_2O_2 (2.56 mL, 25.60 mmol) and LiOH.H_2O (0.54 g, 12.80 mmol) at 0℃. The mixture was stirred for 1 h at 0℃, then at r.t. for 12 h. Dilution with water, extraction with CH_2Cl_2, evaporation of the dried extracts furnished D-(-)-camphor sultam. The aqueous phase was acidified to pH 1-2 with 1 mol/L HCl, saturated with NaCl and extracted with AcOEt. Drying and evaporation of solvent afforded Mitiglinide (0.94 g, 93%) as a colorless viscous oil.
Compound **1**: mp 146-148℃; $[\alpha]_D^{20}$ -85.6 (c=1.0, $CHCl_3$); ^{1}H-NMR($CDCl_3$, δ ppm): 0.95 (s, 3H), 1.08 (s, 3H), 1.34-1.42 (m, 2H), 1.85-1.90 (m, 3H), 2.05-2.07 (d, 2H, *J* = 8.24 Hz.), 2.97-3.07 (m, 4H), 3.40-3.50 (m, 2H), 3.84-3.88 (t, 1H, *J* = 6.32 Hz.), 7.17-7.30 (m, 5H); MS (70 eV): *m/z* 347(M^+, 72%), 133(41%), 105(100%), 91(81%). Anal. Calcd. for $C_{19}H_{25}NO_3S$: C 65.68, H 7.25, N 4.03; Found: C 65.80, H 7.06, N 4.00.
mitiglinide: $[\alpha]_D^{20}$ –3.5 (c 1.0, MeOH); ^{1}H-NMR($CDCl_3$, δ ppm): 1.23-1.63 (m, 8H), 2.13-2.22 (m, 2H), 2.42-2.52 (m, 2H), 2.73-3.32 (m, 7H), 7.18-7.32 (m, 5H); ESI-MS: *m/z* 316.15 $(M+H)^+$; Anal. Calcd. for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; Found: C 72.51, H 8.03, N 4.31.
KAD-1229: mp 179-185℃ (Lit.[2] 179-185℃); $[\alpha]_D^{20}$ +5.4 (c 0.6, MeOH) (Lit.[2]+5.7, C 1.0, MeOH); ESI-MS: *m/z* 669.32 $(M-2H_2O+H)^+$; ^{1}H-NMR($CDCl_3$, δ ppm): 1.13-1.39 (m, 16H), 2.0-2.3 (m, 6H), 2.54-2.83 (m, 14H), 3.20-3.22 (m, 6H), 7.11-7.28 (m, 10H); Anal. Calcd. for $C_{38}H_{48}CaN_2O_6.2H_2O$: C 64.75, H 7.44, N 3.94; Found: C 64.46, H 7.35, N3.73.
Analysis of the enantiomeric excess was performed by HPLC with a Chiralcel AS column (25×250 mm, flow rate 0.7 mL/min, UV 214 nm, *n*-hexane/*i*-PrOH=80:20 V/V as the eluent).

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