An Effective and Convenient Method for the Preparation of *KAD-1229*

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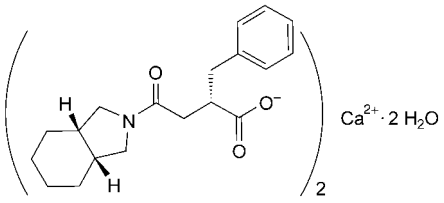
A new convenient method for the asymmetric synthesis of the potent hypoglycemic agent *KAD-1229* was developed. The key step of this method is diasteroselective alkylation of **1** to give crude **2** (d.e. > 93%) in good yield with the easily available *Oppolzer*'s camphorsultam as chiral auxiliary. The overall yield of the product was 57%.

Introduction. – *KAD-1229* (Mitiglinide calcium dihydrate = calcium bis{(2*S*)-4-[(3a*R*,7a*S*)-octahydro-2*H*-isoindol-2-yl]-4-oxo-2-(phenylmethyl)butanoate} dihydrate), a novel hypoglycemic agent with a chemical structure different from that of the sulfonylureas, exhibits a more-rapid-onset but shorter-lived hypoglycemic effect than the sulfonylureas. Like the sulfonylureas, *KAD-1229* inhibits the ATP-sensitive potassium channels in pancreatic β-cells and stimulates insulin release [1]. The configuration of the stereogenic C-atom in the succinyl moiety is very important for the activity of the compound, and the absolute (*S*)-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, and is expected to be launched in near future. The synthesis of *KAD-1229* has been accomplished by several related methods that involve optical resolution [2], asymmetric synthesis by means of *Evans* chiral enolate [2a], and asymmetric hydrogenation with the chiral diphosphine complex of rhodium or ruthenium [3]. However, since the above methods have drawbacks that limit large-scale preparation, we have developed a new effective and convenient method for the preparation of *KAD-1229*.



KAD-1229

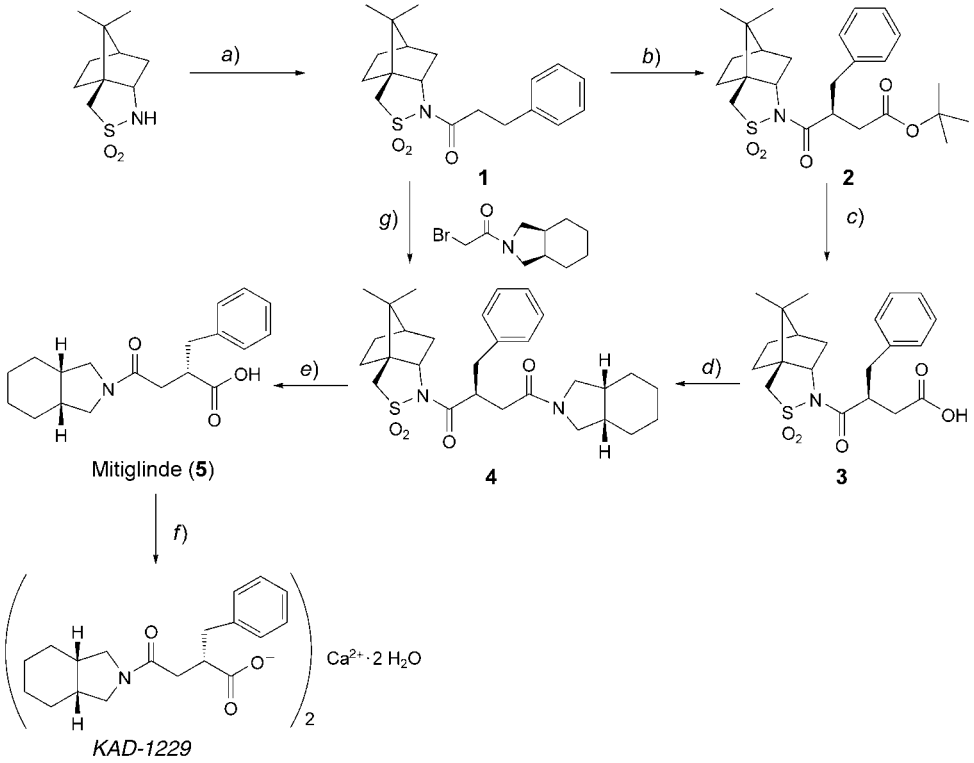
Results and Discussion. – *Oppolzer*'s camphorsultams serve as efficient, versatile, and practical chiral auxiliaries that are easy to prepare from inexpensive camphor. Both enantiomers are currently commercially available in bulk quantities. A highly π-face-selective alkylation of enolate followed by nondestructive removal of the auxiliary affords a highly optically active carboxylic acid. The absolute configuration of the product can easily be directed by a very facile operation, and the products can be purified by crystallization. Recycling of the chiral auxiliary after removal is practical. This method is suitable for scaleable manufacture of pharmaceutical grade *KAD-1229*.

The process for the preparation of *KAD-1229* starts from (−)-camphorsultam (=(3a*S*)-8,8-dimethylhexahydro-3a,6-methano-2,1-benzisothiazole 2,2-dioxide), readily available in 85% yield from (+)-D-camphor [4]. Treatment of (−)-camphorsultam with excess 3-phenylpropionyl chloride in the presence of NaH in toluene at room temperature gave **1** in 91% yield (*Scheme*) [5]. An alternative procedure is to reflux camphorsultam with 1.1 to *ca.* 1.5 equiv. of 3-phenylpropionyl chloride in MeCN for 8–10 h [6]. The crude product, acylsultam **1**, purified by recrystallization from EtOH/H_2O in 89% yield, was reacted with an equimolar amount of base to form the chiral enolate in dry ice/EtOH bath, followed by C(α)-re-alkylation [7] with *tert*-butyl bromoacetate to give **2**. The choice of the organic base was very important: the reaction with BuLi, lithium diisopropylamide (LDA), or NaHMD (sodium hexamethyldisilazane) gave **2** in 30–40%, 60%, or 90% yield, respectively, after recrystallization from MeOH. Alkylation promoted by these bases tends to give products with high diastereoselectivity, and the diastereoisomeric purity of crude product **2** was determined to be >93%. However, the reaction with NaHMDS as the base proceeded smoothly in high yield. The *tert*-butyl ester **2** was cleaved with TFA (CF_3COOH) in CH_2Cl_2 to give the free acid **3** in 87% yield [8]. Acylation of (3a*R*,7a*S*)-octahydro-1*H*-isoindole with **3** by a mixed anhydride method afforded **4** in 84% yield [9]. Compound **4** can be also obtained in 85% yield *via* direct alkylation of **1** with (3a*R*,7a*S*)-2-(bromoacetyl)octahydro-1*H*-isoindole; however, the yield of the (2-bromoacetyl)octahydro-1*H*-isoindole prepared from 2-bromoacetyl bromide and *cis*-octahydro-1*H*-isoindole was only 40%. Nondestructive cleavage of **4** by hydroperoxide-assisted saponification (LiOH, aq. H_2O_2, THF, r.t.) regenerated the camphorsultam (96% recovered yield) and gave mitiglinide (**5**) in 93% yield and high enantiomeric excess (>99% by HPLC analysis of the corresponding methyl ester) [7]. Product **5** was treated with 2N NaOH, followed by treatment with $CaCl_2$. Recrystallization from aqueous EtOH gave *KAD-1229* in 91% yield, with a melting point and specific rotation data identical to those in the literature [2b].

Conclusions. – We describe herein an effective and facile asymmetric synthesis of *KAD-1229* from *Oppolzer*'s camphorsultam with an asymmetric alkylation as the key step. The overall yield of the six-step synthesis was 57%.

We thank Dr. *X. Xu* (Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences) for performing HLPC. This research was supported by *Science & Technology Commission* of the Shanghai Municipality (Grant 02QMB1409).

Scheme. *Synthetic Route to* KAD-1229 *from (−)-Camphorsultam*



a) 3-Phenylpropanoyl chloride, NaH, in toluene, r.t.; 91%; or in MeCN, reflux, 10 h; 89%. *b*) NaHMDS, *tert*-butyl bromoacetate, HMPA, THF, −78 to *ca.* 0°, 16 h; 92%. *c*) TFA, CH_2Cl_2; 87%. *d*) NMM, $ClCO_2{}^iBu$, (3a*R*,7a*S*)-octahydro-1*H*-isoindole, CH_2Cl_2; 84%. *e*) LiOH, aq. THF, 30% H_2O_2; 93%. *f*) 2N NaOH, $CaCl_2$, H_2O/EtOH; 91%. *g*) NaHMDS, (3a*R*,7a*S*)-2-(bromoacetyl)octahydro-1*H*-isoindole, HMPA, THF −78 to *ca.* 0°, 16 h; 85%.

Experimental Part

THF was freshly distilled from Na metal/benzophenone ketyl. All other reagents and solvents were used as received without further purification. M.p.: *Büchi* apparatus, uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter at the sodium-D line. ^{1}H-NMR Spectra: *Varian Mercury-400* spectrometer, 400 MHz, in $CDCl_3$; chemical shifts δ in ppm (TMS as internal standard). MS: *Finnigan MAT-95* spectrometer. Elemental analyses: *Vario EL* instrument.

*(3a*S*,6*R*,7a*S*)-Hexahydro-8,8-dimethyl-1-(3-phenylpropanoyl)-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide* (**1**). *Method A:* To a soln. of (−)-camphorsultam (2.20 g, 10.22 mmol) in MeCN (10 ml) under N_2 was added 3-phenylpropionyl chloride (1.90 ml, 12.78 mmol), and the soln. was heated to reflux for 10 h. After the soln. was cooled to ambient temp., the MeCN was removed in *vacuo*. The residue was dissolved in AcOEt and the org. phase was washed with sat. Na_2CO_3 and sat. NaCl soln., dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was recrystallized from MeOH (or AcOEt/hexane) to afford **1** as a white solid (3.16 g, 89%).

Method B: Compound **1** was also obtained in 91% yield according to [5].

Data of **1**: M.p. 146–148° (lit. 153–154° [5]). $[\alpha]_D^{20} = -85.6$ ($c = 1.0$, $CHCl_3$) (lit. $[\alpha]_D^{20} = -78.9$, $c = 1.14$ [5]). ^{1}H-NMR: 0.95 (*s*, 3 H); 1.08 (*s*, 3 H); 1.34–1.42 (*m*, 2 H); 1.85–1.90 (*m*, 3 H); 2.05–2.07 (*m*, 2 H); 2.97–3.07

(*m*, 4 H); 3.40–3.50 (*m*, 2 H); 3.84–3.88 (*m*, 1 H); 7.17–7.30 (*m*, 5 H). EI-MS: 347 (M^+). Anal. calc. for $C_{19}H_{25}NO_3S$ (347.47): C 65.68, H 7.25, N 4.03; found: C 65.80, H 7.06, N 4.00.

*1,1-Dimethylethyl (3*S*)-4-[(3a*S*,6*R*,7a*S*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3a,6-methano-2,1-benzisothiozol-1(4*H*)-yl]-4-oxo-3-(phenylmethyl)butanoate* (**2**). To a soln. of **1** (1.74 g, 5.00 mmol) in THF (15 ml) at −78° under N_2 was added NaHMDS (5.50 ml of a 1M soln. in THF) dropwise over 5 min. The soln. was stirred at −78° for 0.5 h, and a soln. of *tert*-butyl bromoacetate (2.20 ml, 15.00 mmol) and hexamethylphosphoramide (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 soln. was warmed to r.t. and stirred for 4 h. The reaction was quenched with sat. aq. NH_4Cl soln. (20 ml), and the mixture was extracted with ether (3 × 15 ml). The combined org. phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude product (d.e. > 93%). Crystallization from MeOH gave **2** as crystals (2.13 g, 92%). M.p. 128–129°. $[\alpha]_D^{20} = -58.2$ ($c = 1.0$, MeOH). ^{1}H-NMR: 0.95 (*s*, 3 H); 1.09 (*s*, 3 H); 1.37 (*s*, 9 H); 1.40–1.48 (*m*, 2 H); 1.85–2.16 (*m*, 3 H); 2.31–2.69 (*m*, 2 H); 2.99–3.08 (*m*, 4 H); 3.30–3.63 (*m*, 3 H); 3.85–3.94 (*m*, 1 H); 7.20–7.29 (*m*, 5 H). EI-MS: 461 (M^+). Anal. calc. for $C_{25}H_{35}NO_5S$ (461.61): C 65.05, H 7.64, N 3.03; found: C 64.91, H 7.53, N 2.99.

*(3*S*)-4-[(3a*S*,6*R*,7a*S*)-Tetrahydro-8,8-dimethyl-2,2-dioxido-3a,6-methano-2,1-benzthiazol-1(4*H*)-yl]-4-oxo-3-(phenylmethyl)butanoic Acid* (**3**). Compound **2** (2.40 g, 2.60 mmol) was dissolved in CH_2Cl_2 (10 ml) and cooled to 0°. CF_3COOH (10 ml) was added, and the mixture was stirred overnight at r.t. The volatiles were removed under reduced pressure and the residue dissolved in AcOEt (15 ml). The org. phase was washed with 5% $NaHCO_3$ soln. and brine, dried, and evaporated to give **3** (1.88 g, 87%) in sufficient purity to be employed in subsequent steps. M.p. 202–204° (AcOEt/MeOH). $[\alpha]_D^{20} = -99.1$ ($c = 1.0$, MeOH). ^{1}H-NMR: 0.96 (*s*, 3 H); 1.17 (*s*, 3 H); 1.32–1.44 (*m*, 2 H); 1.85–1.92 (*m*, 3 H); 2.00–2.09 (*m*, 2 H); 2.36–2.49 (*m*, 2 H); 2.80–2.87 (*m*, 1 H); 3.37–3.63 (*m*, 4 H); 3.91–3.94 (*m*, 1 H); 7.19–7.31 (*m*, 5 H). EI-MS: 405 (M^+). Anal. calc. for $C_{21}H_{27}NO_5S$ (405.51): C 62.20, H 6.71, N 3.45; found: C 62.32, H 6.65, N 3.38.

*(3a*S*,6*R*,7a*S*)-8,8-Dimethyl-1-[(2*S*)-4-[(3a*R*,7a*S*)-octahydro-2*H*-isoindol-2-yl]-4-oxo-2-(phenylmethyl)butanoyl]hexahydro-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide* (**4**). To a soln. of **3** (1.60 g, 3.95 mmol) in anh. THF (5 ml) were added 4-methylmorpholine (NMM; 0.57 ml, 5.14 mmol) and $ClCO_2{}^iBu$ (0.69 ml, 5.33 mmol) sequentially at −12°. After 5 min, (3a*R*,7a*S*)-octahydro-1*H*-isoindole (0.67 g, 5.33 mmol) was added. After 1 h, the soln. was filtered and the filtrate concentrated. The residual oil was dissolved in AcOEt (20 ml) and washed successively with 10% $NaHSO_4$ and aq. $NaHCO_3$ soln., and brine. The org. layer was dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallized from AcOEt to give **4** (1.70 g, 84%). M.p. 188–190°. $[\alpha]_D^{20} = -59.4$ ($c = 1.0$, MeOH). ^{1}H-NMR: 0.96 (*s*, 3 H); 1.25 (*s*, 3 H); 1.28–1.52 (*m*, 10 H); 1.85–1.95 (*m*, 3 H); 1.98–2.18 (*m*, 4 H); 2.30–2.35 (*m*, 1 H); 2.52–2.72 (*m*, 2 H); 2.96–3.08 (*m*, 2 H); 3.14–3.37 (*m*, 3 H); 3.42–3.57 (*m*, 3 H); 3.99–4.01 (*m*, 1 H); 7.20–7.29 (*m*, 5 H). EI-MS: 512 (M^+). Anal. calc. for $C_{29}H_{40}N_2O_4S$ (512.70): C 67.94, H 7.86, N 5.46; found: C 68.10, H 7.81, N 5.33.

Compound **4** could be also obtained in 85% yield for direct alkylation of **1** from (3a*R*,7a*S*)-2-(bromoacetyl)octahydro-1*H*-isoindole. (This reagent was prepared by addition of a soln. of bromoacetyl bromide (12.06 g in 20 ml MeCN) to a soln. of (3a*R*,7a*S*)-octahydro-1*H*-isoindole (7.51 g in 80 ml MeCN) with cooling at −10° and stirring. After 3 h, the mixture was filtered, and the filtrate was worked up to give 5.91 g (40% yield) of (2-bromoacetyl)octahydro-1*H*-isoindole.)

*(2*S*)-4-[(3a*R*,7a*S*)-Octahydro-2*H*-isoindol-2-yl]-4-oxo-2-(phenylmethyl)butanoic Acid* (= Mitiglinide, **5**). To a soln. of **4** (1.64 g, 3.20 mmol) in 25 ml THF/H_2O 1:1 were added aq. 30% H_2O_2 (2.56 ml, 25.60 mmol) and $LiOH \cdot H_2O$ (0.54 g, 12.80 mmol) at 0°. The mixture was stirred at 0° for 1 h and then at r.t. for 12 h. Dilution with H_2O, extraction with CH_2Cl_2, drying ($MgSO_4$) of the org. phase, and evaporation regenerated the chiral auxiliary camphorsultam. The aq. phase was acidified to pH 1–2 with 1N HCl, sat. with NaCl, and extracted with AcOEt. Drying and evaporation of solvent afford mitiglinide (0.94 g, 93%) as a colorless viscous oil. The ee was determined to be 99.4% by HPLC analysis of the corresponding Me ester on a *Chiralcel AS* column (250 × 4.6 mm, flow rate 0.7 ml/min, UV 214 nm, *n*-hexane/*i*-PrOH 80:20 as the eluent). $[\alpha]_D^{20} = -3.5$ ($c = 1.0$, MeOH). ^{1}H-NMR: 1.23–1.63 (*m*, 8 H); 2.13–2.22 (*m*, 2 H); 2.42–2.52 (*m*, 2 H); 2.73–3.32 (*m*, 7 H); 7.18–7.32 (*m*, 5 H). ESI-MS: 316.15 ($[M+H]^+$). Anal. calc. for $C_{19}H_{25}NO_3$ (315.41): C 72.35, H 7.99, N 4.44; found: C 72.51, H 8.03, N 4.31.

*Calcium Bis{(2*S*)-4-[(3a*R*,7a*S*)-octahydro-2*H*-isoindol-2-yl]-4-oxo-2-(phenylmethyl)butanoate} Dihydrate* (*KAD-1229*). A soln. of mitiglinide (0.81 g, 2.57 mmol) in EtOH (3 ml) was treated with 2N NaOH soln. (1.28 ml, 12.57 mmol). The mixture was evaporated under reduced pressure. The residue was dissolved in H_2O (6 ml), and a soln. of $CaCl_2$ (1.51 g, 10.24 mmol) in H_2O (2 ml) was added, followed by vigorous stirring for 1 h. The mixture was extracted with $CHCl_3$ (5 × 4 ml), the org. layer was washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was recrystallized from 95% EtOH to give *KAD-1229* as

colorless crystals (0.82 g, 91%). M.p. 179–185° (lit. 179–185° [2b]). $[\alpha]_D^{20} = +5.4$ ($c = 0.6$, MeOH) (lit. $[\alpha]_D^{20} = +5.7$, $c = 1.0$, MeOH [2b]). ^{1}H-NMR: 1.13–1.39 (*m*, 16 H); 2.0–2.3 (*m*, 6 H); 2.54–2.83 (*m*, 14 H); 3.20–3.22 (*m*, 6 H); 7.11–7.28 (*m*, 10 H). ESI-MS: 669.32 ($[M - 2\,H_2O + H]^+$). Anal. calc. for $C_{38}H_{48}CaN_2O_6 \cdot 2\,H_2O$ (704.91): C 64.75, H 7.44, N 3.94; found: C 64.46, H 7.35, N 3.73.

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Received March 17, 2004