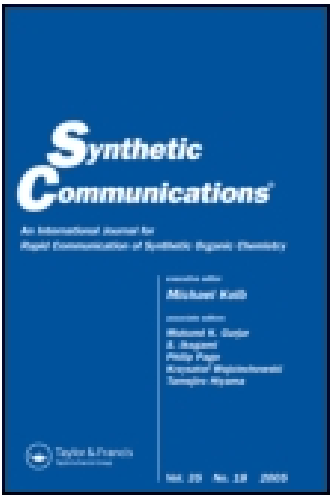

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Practical and Efficient Preparation of (S)-2-Benzylsuccinic Acid: A Key Acid Synthon of KAD-1229

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Published online: 10 Jan 2011.

To cite this article: Jian-Chao Liu , Yu-She Yang & Ru-Yun Ji (2004) A Practical and Efficient Preparation of (S)-2-Benzylsuccinic Acid: A Key Acid Synthon of KAD-1229, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:14, 2633-2640, DOI: 10.1081/SCC-200025625

To link to this article: http://dx.doi.org/10.1081/SCC-200025625

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 14, pp. 2633–2640, 2004

A Practical and Efficient Preparation of (*S*)-2-Benzylsuccinic Acid: A Key Acid Synthon of KAD-1229

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ABSTRACT

This report describes a practical and an efficient synthesis of (*S*)-2-benzylsuccinic acid, which was employed as a key intermediate for hypoglycemic KAD-1229 by means of asymmetric alkylation of *N*-acylsultam. The condensation of D-(−)-camphorsultam with 3-phenylpropionyl chloride gave *N*-acylsultam **1**. *N*-acylsultam **1** reacted with 1.1 equimolar amount of sodium amide base to form chiral enolate, followed by alkylation with *tert*-butyl bromoacetate to afford **2**. Cleavage of ester and

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DOI: 10.1080/SCC-200025625 0039-7911 (Print); 1532-2432 (Online)

saponification with H_2O_2–LiOH provided the desired compound **5** with excellent yield and high optical purity.

Key Words: KAD-1229; (*S*)-2-Benzylsuccinic acid; Camphorsultam.

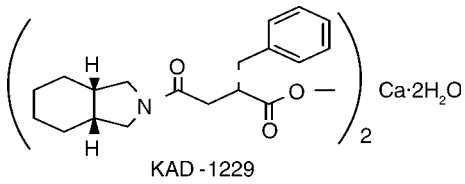
INTRODUCTION

KAD-1229 (Fig. 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 compared with sulfonylureas. KAD-1229 inhibits the ATP-sensitive potassium channels in pancreatic β-cell and stimulates insulin secretion like sulfonylureas.[1] The stereochemistry of the asymmetric carbon in the propionyl group is very important for the activity of the compound and the (*S*)-absolute configuration is necessary for the insulin secretory effect.

Recently, KAD-1229 has been in phase III clinical trials in Japan and in phase II clinical trials in Europe and in the USA for the treatment of type 2 diabetes and expected to be launched in near future. Two different procedures were used to obtain KAD-1229 from (*S*)-2-benzylsuccinic acid (Schs. 1 and 2).[2] The preparation of (*S*)-2-benzylsuccinic acid has been reported previously by means of catalytic asymmetric hydrogenation.[3] We report here a practical and an efficient synthetic strategy for the preparation of (*S*)-2-benzylsuccinic acid by using Oppolzer's camphorsultam as chiral auxiliary with 68% overall yield and high optical purity.

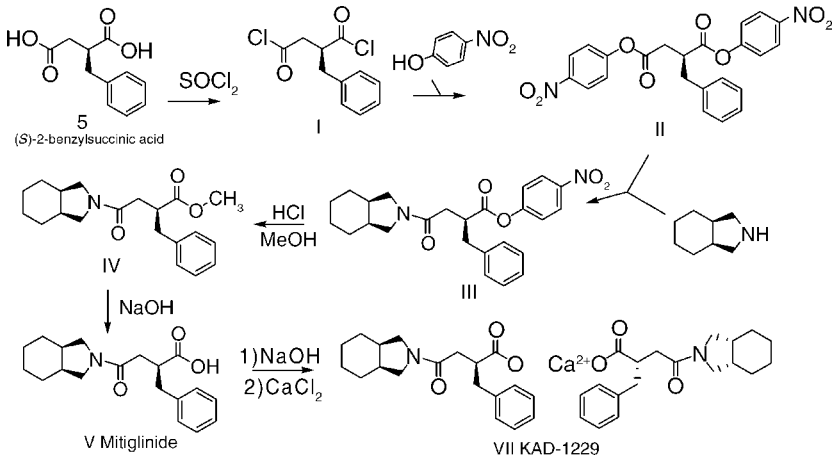
RESULTS AND DISCUSSION

Stobbe condensation of benzaldehyde with diethyl succinate and saponification led to benzylidenesuccinic acid. Asymmetric hydrogenation for the preparation of benzylsuccinic acid according to the literatures required a chiral diphosphine complex of rhodium or ruthenium such as $Ru_2Cl_4((+)\text{-BINAP})_2(NEt_3)$, RuHCl $((+)\text{-BINAP})_2$, and $Rh(COD)Cl_2$(MOD-



KAD-1229

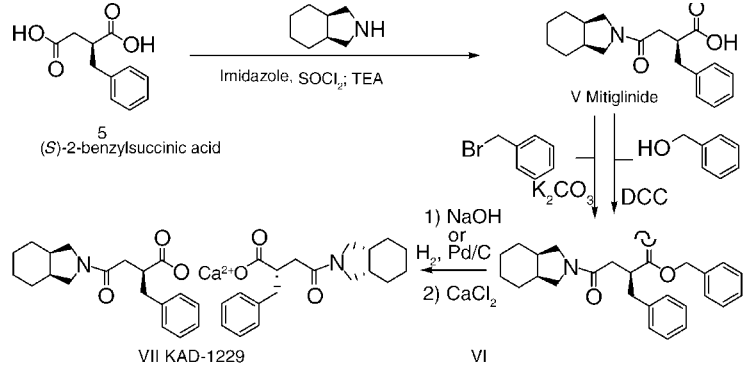
Figure 1. Structure of KAD-1229.



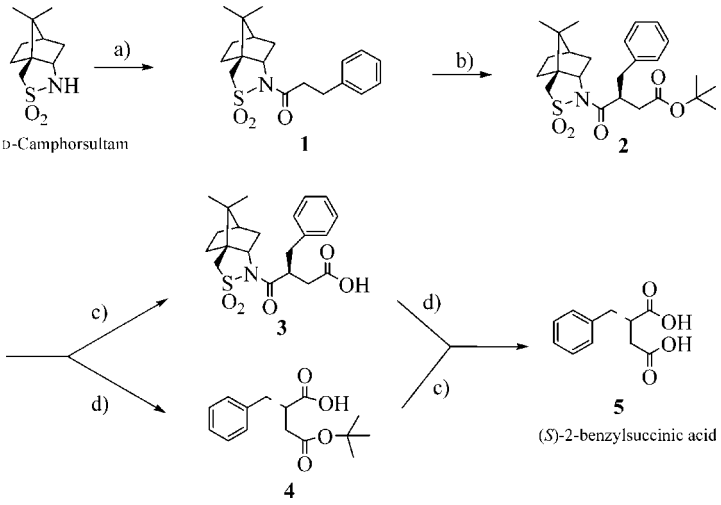
Scheme 1.

DIOP).[3] The highest ee was noted about 90% in the productions, however these chiral catalysts are unstable and expensive.

We considered Oppolzer's camphorsultam served as efficient, versatile, and practical chiral auxiliary. A highly π-face-selective alkylation of enolates followed by nondestructive removal of the auxiliary afforded a highly optically active carboxylic acid. The products could be purified by crystallization. Recycling of the auxiliary after removal is often practical. The process for the preparation of (*S*)-2-benzylsuccinic acid (Sch. 3) starts from D-(−)-camphorsultam, readily available in 85% yield from the



Scheme 2.



Scheme 3. Reagents and conditions: (a) NaH, tol., r.t., 91% or CH_3CN, refluxing, 10 hr, 89%; (b) NaHMDS, *tert*-butyl bromoacetate, HMPA, THF, −78–0°C, 16 hr, 92%; (c) TFA, CH_2Cl_2, 87–100%; (d) LiOH, aqueous THF, 30% H_2O_2, 93%.

natural D-camphor.[4] Treatment of D-(−)-camphorsultam with an excess of 3-phenylpropionyl chloride in the presence of NaH in toluene at room temperature gave **1** in 91% yield.[5] An alternative procedure was performed by refluxing D-(−)-camphorsultam with 1.1–1.5 equimolar 3-phenylpropionyl chloride in CH_3CN for 8–10 hr.[6] The crude product was then easily purified by recrystallization from EtOH/H_2O in 89% yield. Acylsultam **1** reacted with the organic base in THF to form chiral enolate in dry ice/ethanol bath, followed by alkylation with *tert*-butyl bromoacetate to give **2**. We next examined the effects of the organic base. The reaction was performed using *n*-BuLi as base and gave the desired alkylated production in about 30–40% yield. Under the same conditions, the reaction using lithium diisopropylamine (LDA) or sodium hexamethyldisilazide (NaHMDS) gave the product **2** in 60% and 92% yield recrystallized from methanol, respectively. Alkylation process employing these bases has exhibited high diastereoselectivity and diastereomeric purity of crude product **2**, determined to be more than 93%. However, the reaction using NaHMDS as base proceeded smoothly in high yield. The ester **2** was cleaved by using TFA in dichloromethane, giving the free acid **3** in 87% yield.[7] Nondestructive cleavage of compound **3** by hydroperoxide-assisted saponification (LiOH, aq. THF, r.t.) gave sultam (96% recovery yield) and **5** in 93% yield. Finally, the order of cleavages of ester and chiral auxiliary did not affect the yield and the purity of product **5**. The

overall yield of four step reaction was 68% and the optical purity was more than 99% (calculated on the basis of the maximum optical rotation $[\alpha]_D^{20} = -27.0$ (*c* 2.0, EtOAc) for the pure S-enantiomer).[8]

In conclusion, an efficient and practical preparation of (*S*)-2-benzylsuccinic acid has been developed. The absolute stereochemistry was controlled by use of D-(−)-camphorsultam chiral auxiliary.

EXPERIMENTAL SECTION

Melting points were measured with BÜCHI melting point apparatus and were uncorrected. Mass spectra were taken using Finnigan MAT-95 spectrometer. ^{1}H-NMR spectra were recorded on Varian Mercury 400 NMR spectrometer in $CDCl_3$ unless otherwise stated, and chemical shifts were reported in δ (TMS as internal standard). Elemental analyses were performed on Vario EL instrument. Optical rotations were taken with Perkin–Elmer 241 Polarimeter at the sodium D line. THF was freshly distilled from sodium metal/benzophenone ketyl. All other reagents and solvents were used as received without further purification.

N-(3-Phenylpropionyl)(2*R*)-bornane-10,2-sultam

Method A: To a solution of 1(*S*)-(−)-2,10-bornane sultam (2.20 g, 10.22 mmol) in CH_3CN (10 mL) under nitrogen, 3-phenylpropionyl chloride (1.90 mL, 12.78 mmol) was added and the solution was heated to reflux for 10 hr. After the solution was cooled to ambient temperature, the CH_3CN was removed in vacuo. The residue was diluted with EtOAc and the organic phase was washed with saturated Na_2CO_3 and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The crude product was recrystallized from methanol (or EtOAc/hexane) to afford **1** as a white solid (3.16 g, 89%).

Method B: A suspension of 60% sodium hydride (0.60 g, 15.00 mmol) in toluene (25 mL) was treated with a solution of (1*S*,2*R*)-(−)-10,2-bornane sultam (2.15 g, 10.00 mmol) in dry THF (15 mL). The mixture was stirred for 1 hr. 3-Phenylpropionyl chloride (2.23 mL, 15.00 mmol) in THF (5 mL) was added over 20 min and the mixture was stirred for 16 hr. Saturated aqueous ammonium chloride (15 mL) was added and the mixture was poured into ether (50 mL); the separated aqueous layer was washed with ether (25 mL × 2). The combined organic extracts were washed with portions (10 mL × 3) of water and brine and dried ($MgSO_4$). Evaporation of the solvent gave a white solid which was re-crystallized from methanol to afford **1** (3.15 g,

91%): m.p. 146–148°C, $[\alpha]_D^{20} = -85.6$ (c 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ:=0.95 (3H, s), 1.08 (3H, s), 1.34–1.42 (2H, m), 1.85–1.90 (3H, m), 2.05–2.07 (2H, d), 2.97–3.07 (4H, m), 3.40–3.50 (2H, m), 3.84–3.88 (1H, t), 7.17–7.30 (5H, m); MS (70 eV) m/z (%): 347 (M^+, 72), 133 (41), 105 (100), 91 (81). Calculated 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.

N-[2-(*S*)-*tert*-Butoxycarbonylmethyl-3-phenylpropionyl]-(2*R*)-bornane-10,2-sultam(2)

A cooled solution of compound **1** (1.74 g, 5.00 mmol) in THF (15 mL) at −78°C (all under nitrogen) was treated with NaHMDS (5.50 mL, 1 M solution in THF) over 5 min dropwise. The mixture was stirred at −78°C for 0.5 hr, the 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. The mixture was allowed to be warmed to r.t. over 16 hr and then was stirred at 25°C for 4 hr. Saturated aqueous NH_4Cl (20 mL) was added to stop reaction and the mixture was extracted with ether. The combined organic layer was washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave crude product which crystallized from methanol to give **2** as crystals (2.13 g, 92%): m.p. 128–129°C, $[\alpha]_D^{20} = -58.2$ (c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.95 (3H, s), 1.09 (3H, s), 1.37 (9H, s), 1.40–1.48 (2H, m), 1.85–2.16 (3H, m), 2.31–2.69 (2H, m), 2.99–3.08 (4H, m), 3.30–3.63 (3H, m), 3.85–3.94 (1H, m), 7.20–7.29 (5H, m); MS (70 eV) m/z (%): 461 (M^+, 8), 347 (52), 133 (38), 105 (100). Calculated for $C_{25}H_{35}NO_5S$: %C 65.05, %H 7.64, %N 3.03. Found: %C 64.91, %H 7.53, %N 2.99.

N-[2-*(S)*-Carbonylmethyl-3-phenylpropionyl]-(2*R*)-bornane-10,2-sultam

2 (1.20 g, 2.60 mmol) was dissolved in CH_2Cl_2 (10 mL) and=cooled to 0°C. Trifluoroacetic acid (5 mL) was added and the mixture was stirred overnight at room temperature. The volatiles were removed at reduced pressure and the residue was dissolved in ethyl acetate (15 mL). The organic phase was washed with 5% $NaHCO_3$ and brine, dried and evaporated to give **3** (0.94 g, 87%) with sufficient purity to be employed in subsequent steps: m.p. 202–204°C, $[\alpha]_D^{20} = -99.1$ (c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.96 (3H, s), 1.17 (3H, s), 1.32–1.44 (2H, m), 1.85–1.92 (3H, m), 2.00–2.09 (2H, m), 2.36–2.49 (2H, m), 2.80–2.87 (1H, m), 3.37–3.63 (4H, m), 3.91–3.94 (1H, m), 7.19–7.31 (5H, m); MS (70 eV) m/z (%): 405

(M^+, 12), 347 (56), 105 (100). Calculated for $C_{21}H_{27}NO_5S$: %C 62.20, %H 6.71, %N 3.45. Found: %C 62.32, %H 6.65, %N 3.38.

(*S*)-3-(*tert*-Butoxycarbonyl)-2-benzylpropanoic Acid (4)

2 (1.00 g, 2.17 mmol) was dissolved in THF (9 mL), the solution of 1N LiOH (8.67 mL, 4 equimolar) and 30% H_2O_2 (1.77 mL, 8 equimolar) were added sequentially at 0°C. After 1 hr, the mixture was warmed to room temperature and stirred for overnight. The mixture was diluted with water and extracted with CH_2Cl_2. The aqueous phase was acidified to pH = 1–2 with 1 N HCl, saturated with NaCl and extracted with EtOAc. Drying ($MgSO_4$) of the organic phase and evaporation of the solvent afforded **4** with sufficient purity to be employed in subsequent steps: (0.48 g, 84%): m.p. 119–120°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.41 (9H, s), 2.32–2.37 (1H, dd, $J = 2.3$, 8.4 Hz), 2.52–2.59 (1H, m), 2.73–2.79 (1H, m), 3.07–3.13 (2H, m), 7.19–7.33 (5H, m); MS m/z (%, ESI): 287.0 $(M + Na)^+$, 263.1 $(M - H)^-$.

(*S*)-2-Benzylsuccinic Acid (5)

Method A: Aqueous (30%) H_2O_2 (1.60 mL, 16.00 mmol) and $LiOH \cdot H_2O$ (0.34 g, 8.00 mmol) were added at 0°C to a solution of **3** (0.81 g, 2.00 mmol) in THF/H_2O (16 mL, 1 : 1). The mixture was stirred at 0°C for 1 hr and then at r.t. for 12 hr. Dilution with water, extraction with CH_2Cl_2, drying ($MgSO_4$) of the organic phase, and evaporation furnished with camphor. The aqueous phase was acidified to pH = 1–2 with 1 N HCl, saturated with NaCl, and extracted with EtOAc. The combined organic layer was dried ($MgSO_4$) and concentrated at reduced pressure. Crystallization with EtOAc afforded **5** (0.39 g, 93%).

Method B: **4** (0.44 g, 1.66 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. The trifluoroacetic acid (2.5 mL) was added and the mixture was stirred overnight at room temperature. The volatiles were removed at reduced pressure and the residue was dissolved in ethyl acetate (15 mL). The organic phase was washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated at reduced pressure afforded **5** with a mostly quantitative yield (0.34 g): m.p. 163–164°C, $[\alpha]_D^{20} = -27.0$ (*c* 2.0, EtOAc) (Lit.[8] 164.5°C, $[\alpha]_D^{20} = -27.0$ (*c* 2.0, EtOAc)); ^{1}H-NMR (CD_3OD, 400 MHz) δ: 2.25 (1H, dd, $J = 16.8$, 4.4 Hz), 2.47 (1H, dd, $J = 16.8$, 9.2 Hz), 2.72 (1H, dd, $J = 12.4$, 5.6 Hz), 2.90–2.97 (2H, m), 7.09–7.20 (5H, m); MS m/z (%, ESI): 231.0 $(M + Na)^+$, 207.1 $(M - H)^-$. Calculated for $C_{11}H_{12}O_4$: %C 63.45, %H 5.81. Found: %C 63.69, %H 5.76.

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Received in Japan January 19, 2004