Organic Process Research & Development **2009**, *13,* 463–467

Efficient Synthesis of (2*S*,3*S*)-2-Ethyl-3-methylvaleramide Using (1*S*,2*S*)-Pseudoephedrine as a Chiral Auxiliary

Bin-Feng Li,* Robert M. Hughes, Jackie Le, Kevin McGee, Donald J. Gallagher, Raymond S. Gross, David Provencal, Jayachandra P. Reddy, Peng Wang, Lev Zegelman, Yuxin Zhao, and Scott E. Zook

Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, California 92130, U.S.A.

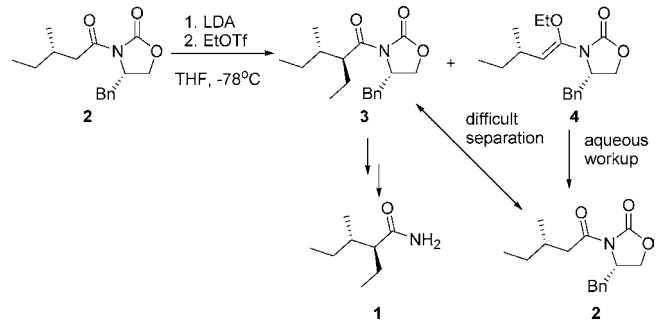
Abstract:

An efficient and scaleable synthesis of (2*S*,3*S*)-2-ethyl-3-methylvaleramide (1) has been developed starting from inexpensive and readily available L-isoleucine. The key step in this process is an asymmetric alkylation using (1*S*,2*S*)-pseudoephedrine as a chiral auxiliary. A practical procedure was developed to remove the sterically hindered pseudoephedrine auxiliary from the amide. The process consists of eight chemical steps and five isolations without any chromatographic purification. It has been successfully implemented to prepare several multikilogram batches of the target compound 1 in 41% overall yield.

Introduction

Valnoctamide (2-ethyl-3-methylvaleramide, Nirvanil, VCD) is used clinically as a mild tranquilizer in several European countries.[1] Valnoctamide contains two stereogenic carbon atoms and is produced commercially as a mixture of four stereoisomers. Bialer and co-workers have demonstrated that the diastereomers and enantiomers of VCD exhibit different pharmacokinetic profiles in healthy subjects and epileptic patients.[2] Our preclinical testing showed that the (2*S*,3*S*)-2-ethyl-3-methylvaleramide isomer (**1**) is more potent and selective in various pain and seizure models. Neurocrine's development efforts have been focused on **1** in accordance with the preferences of regulatory agencies for single enantiomer drugs.[3]

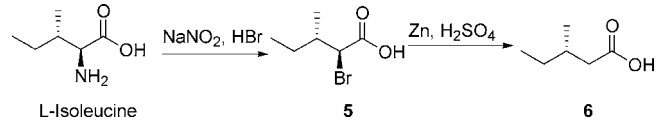
Although **1** has a relatively simple constitution, the presence of two contiguous alkyl asymmetric centers ensures a significant synthetic challenge. Bialer and co-workers did report a stereoselective synthetic method of both stereoisomers using chiral oxazolidinone auxiliaries.[4] This synthesis required the use of the highly reactive and expensive alkylating agent ethyl triflate due to the low nucleophilicity of the enolate. During the alkylation step, the ratio of desired *C*-alkylated product **3** to *O*-alkylated byproduct **4** was ~1:1. Upon aqueous workup, **4** was converted back to the starting material **2**, which was very difficult to separate from the desired product even by flash chromatography. This approach was only suitable to fulfill a short-term need for a few grams of material.



In order to further elucidate the pharmacokinetic profile and toxicological effects of **1**, several kilograms of material were required. Thus, a practical, efficient, and scaleable synthesis method was needed. Our approach was centered on the replacement of the oxazolidinone auxiliary with a suitable substitute that obviated the need for cryogenic temperatures and chromatographic purification. In this contribution we report our success in optimizing and scaling up the asymmetric alkylation using pseudoephedrine as the chiral auxiliary.

Results and Discussion

Inexpensive and readily available L-isoleucine was used as the starting material for our synthesis. The key intermediate (3*S*)-methylvaleric acid **6** was synthesized as shown below, utilizing a literature procedure.[4] L-Isoleucine underwent diazotization in HBr followed by the reduction of the resultant bromo-acid **5** with zinc and H_2SO_4 to provide **6**.[5] The throughput of the zinc reduction was improved by using higher concentration H_2SO_4 with no significant effect on product yield or purity. Acid **6** was isolated by vacuum distillation in 78% yield overall yield.



Acid **6** was reacted with pivaloyl chloride in CH_2Cl_2 in the presence of Et_3N to form the corresponding mixed anhydride, which reacted in situ with (1*S*,2*S*)-pseudoephedrine to give amide **7**. (1*S*,2*S*)-Pseudoephedrine was added as a solid in order to minimize the reaction volume. This conversion proceeded smoothly with <1% of *N*,*O*-diacylated byproduct detected by

* To whom correspondence should be addressed. E-mail: bli@neurocrine.com. Telephone: +1-858-617-7827. Fax: +1-858-617-7717.

(1) Reynolds, J. E. F. In *Martindale: The Extra Pharmacopoeia*, 31st ed.; Pharmaceutical Press: London, 1996; p 742.
(2) Barel, S.; Yagen, B.; Schurig, V.; Soback, S.; Pisani, F.; Perucca, E.; Bialer, M. *Clin. Pharmacol. Ther.* **1997**, *61*, 442–449.
(3) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.
(4) (a) Roeder, M.; Spiegelstein, O.; Schurig, V.; Bialer, M.; Yagen, B. *Tetrahedron: Asymmetry* **1999**, *10*, 841. (b) Bialer, M.; Yagen, B.; Spiegelstein, O.; Roeder, M.; Schurig, V. PCT Int. Appl. 9830536, 1998.

(5) It should be noted that careful handling of compound **6** is required due to the stench associated with it. (3*S*)-Methylvaleric acid **6** is also commercially available from AstaTech Inc. and other companies.

10.1021/op800260j CCC: $40.75
Published on Web 01/30/2009

Table 1. **Asymmetric alkylation using (1*S*,2*S*)-pseudoephedrine as the chiral auxiliary[a]**

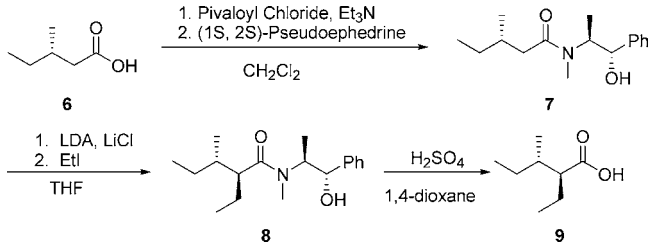
entry	LiCl (equiv)	THF volume (L/mol)	temperature (°C)	conversion (%)	purity (%)	dr (2*S*:2*R*)
1	6	6.0	−78,23,0	>99	97.5	97.6:2.4
2	6	6.0	−20,23,0	>99	97.6	97.5:2.5
3	6	6.0	−20,23,0	98.6	97.3	96.8:3.2
4	4	6.0	−20,23,0	90	83.4	93.6:3.4
5	4	3.5	−20,23,0	>99	97.6	97.2:2.8
6	2	1.5	−20,23,0	>99	97.3	97.1:2.9
7	1	1.0	−20,23,0	>99	97.5	97.0:3.0
8	2	1.5	−15 ±5	>99	>99	96.5:3.5
9	2	1.5	−15 ±5	>99	>99	96.1:3.9

[a] All reactions were at 10 mmol scale under inert atmosphere, except entry 3 (10 mol) and entry 9 (20 mol). The chemical purity was determined by LC−MS with two major impurities (amide **7** and bis-alkylation). Diastereomeric ratio (dr) was determined by chiral GC analysis.

HPLC. Amide **7** was used as a THF solution in the next step without any purification after simple workup.

The alkylation reaction was first attempted on 10 mmol scale following the original protocol reported by Myers and co-workers.[6] The enolate dianion was formed by treatment with LDA (2.3 equiv) in THF in the presence of 6 equiv of LiCl using a temperature cycle (−78 °C for 1 h, 0 °C for 15 min, 23 °C for 5 min, 0 °C for alkylation) followed by the addition of 1.5 equiv of EtI. HPLC analysis indicated <0.5% of starting material (amide **7**), 97.5% of product (amide **8**), and about 2% of a single byproduct (M + 28, postulated to be the *O*-alkylation of the secondary hydroxyl group of the pseudoephedrine auxiliary). Chiral GC analysis indicated that the diastereomeric ratio (dr) was 97.6:2.4 (Table 1, entry 1). This acceptable but relatively low diastereoselectivity is apparently the result of mismatched asymmetric induction between the chiral center at the 3-position of the acid moiety and the (1*S*,2*S*)-pseudoephedrine stereochemistry. When (1*R*,2*R*)-pseudoephedrine was used, the diastereoselectivity of this alkylation reaction was greater than 99% de to give the (2*R*,3*S*)-diastereomer of amide **8**.

Scheme 1. **Synthesis of (2S,3S)-2-ethyl-3-methyl-valeric acid (9)**



With this promising result in hand, we desired to optimize the reaction for scale-up. One obvious challenge in scale-up of this procedure was the low temperature (−78 °C). Although cryogenic reactions are feasible on scale, use of these processes is more expensive and complex and limits the number of potential manufacturing sites. Furthermore, our kilo-laboratory jacketed reactors have a practical operating lower limit of −30 °C, and we desired to perform this initial work in-house due to timing and cost reasons. Considering these thermal constraints, a reaction was piloted starting at −20 °C, then followed with the same warm-up and cool-down procedure, and an identical result was obtained (Table 1, entry 2). This reaction was scaled up to 10 mol scale. Over 99% conversion was achieved with an acceptable diastereoselectivity (96.8:3.2 dr) (Table 1, entry 3). During this run, we had some problems during the workup. A large amount of an inorganic salt crashed out during the concentration of the final organic solution in spite of two aqueous washes. This was thought to be LiCl, which is reasonably soluble in THF and was extracted into the organic layer.

During our optimization experiments, we sought to reduce the equivalents of LiCl used. When 4 equiv instead of 6 equiv were used under otherwise identical conditions, the reaction stalled at ∼90% conversion and produced 6% of the bis-alkylation byproduct (Table 1, entry 4), similar to the original report.[6] We noticed that solid LiCl was visible when the solution warmed up to 23 °C with 6 equiv of LiCl, but not with 4 equiv. This led us to evaluate whether the absolute LiCl stoichiometry or concentration was important. When the THF amount was reduced proportionally (maintaining LiCl saturation even at 23 °C), we were pleased to discover that the reaction went to completion and cleanly gave the product with similar diastereoselectivity (Table 1, entry 5). The amount of LiCl could be further reduced to 1 equiv (Table 1, entry 7). For operational convenience, 2 equiv was used in subsequent campaigns. At the same time, the amount of THF was reduced from 6.0 L/mol to 1.50 L/mol.

Another less than ideal processing issue was the use of multiple temperature ramps. Temperature ramping for a small laboratory reaction is relatively quick and easy but can take several hours per ramp for a large-scale reaction. Upon further optimization, the reaction could be run at −15 ± 5 °C with no effect on conversion or diastereoselectivity (Table 1, entry 8). The bis-alkylation byproduct was also reduced to <0.5% using these conditions.

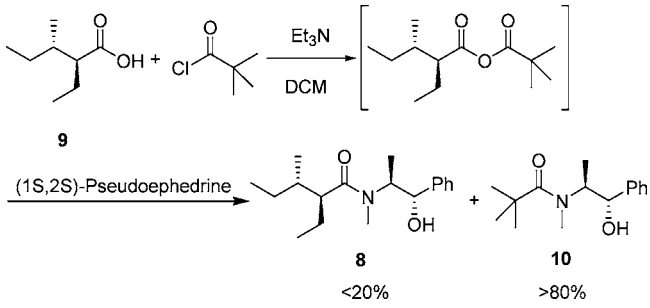
The reduction of LiCl and THF amount significantly increased the reaction throughput from about 11 L/mol to 4.5 L/mol. These changes also avoided salt precipitation during the workup or concentration, making the process operationally easier. This optimized procedure gave excellent conversion and diastereoselectivity at 20 mol scale (Table 1, entry 9) in a 100 L reactor. Amide **8** was then used as a 1,4-dioxane solution (50 w/w %) in the next step without further purification.

(6) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.

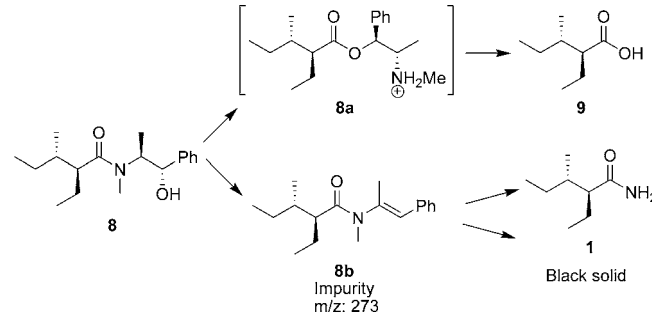
We first attempted the amide hydrolysis using literature conditions with 4 M H_2SO_4 in refluxing dioxane.[6] Surprisingly, the hydrolysis of amide **8** would not go to completion even after a week. When 9 M H_2SO_4 was used, it was complete overnight. However, the isolated yield of acid **9** was <30%, and a large amount of black precipitate formed, which coated the reactor walls and complicated the workup. The hydrolysis of amide **8** with NaOH in a 2:1:1 mixture of H_2O, MeOH, and *tert*-butyl alcohol[6] was also very slow and afforded acid **9** in significantly lower diastereomeric purity (~75:25).

These results are consistent with literature reports in which the hydrolysis of α,β-disubstituted pseudoephedrine amides under acidic conditions was found to be strongly dependent on the steric demands of α-alkyl substituents.[7] In our case, amide **7** can be hydrolyzed to the corresponding acid **6** in 92% yield by heating in 4 M H_2SO_4 for 5 h, whereas hydrolysis of α-substituted **8** to **9** is problematic.

Another illustration of the effect of α-substitution is provided by comparison of mixed anhydride-based reactions of acids **6** and **9**. Preparation of the mixed anhydride of **6** and reaction with (1*S*,2*S*)-pseudoephedrine provided the expected amide with only traces of amide **10** derived from addition to the pivaloyl carbonyl group. However, preparation of the mixed anhydride of **9** and reaction with (1*S*,2*S*)-pseudoephedrine produced a 20:80 mixture of the desired amide **8** and amide **10**.

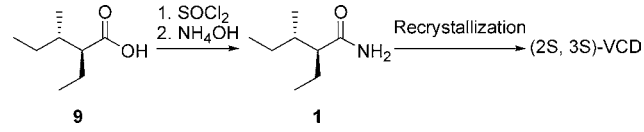


The mechanism of pseudoephedrine amide hydrolysis is well-documented in the literature.[6,7] Under acidic conditions, a fast N to O acyl-transfer process occurs followed by rate-determining hydrolysis of the intermediate ester. Careful monitoring of the hydrolysis reaction of amide **8** showed that the normally fast intramolecular N to O acyl transfer reaction was slow, presumably due to the strong steric hindrance at that carbonyl position. Using 4 M H_2SO_4, it took more than 4 h to complete this intramolecular acyl transformation, whereas use of 9 M H_2SO_4 provided reaction completion in <1 h. However, there was a substantial impurity formed with *m*/*z* 273 (M − 18) under these concentrated conditions. This impurity is believed to be dehydrated amide **8b**. Ammonium ester **8a** is converted to acid **9** upon further heating while we believe **8b** is converted to the black, polymerized solid. Trace amounts of amide **1** were also detected that presumably arise via hydrolysis of enamine **8b**.[8]



The following procedure was developed to complete the hydrolysis in a shorter time and obtain an improved yield: Amide **8** was first refluxed (~90 °C) in 3 M H_2SO_4 until over 90% of amide **8** had converted to the ammonium ester **8a**. Performing the **8** to **8a** conversion using less concentrated acid minimized the amount of **8b** formation and subsequent polymerization. Concentrated H_2SO_4 was then added to adjust the H_2SO_4 concentration in the reactor to 9 M (reflux temperature ~125 °C) to speed up the hydrolysis of **8a** to acid **9**. Using this modified protocol, the hydrolysis of **8** to **9** was complete in 24 h. Acid **9** was obtained in 76% overall yield from acid **6** after acid/base extracts. The diastereomeric purity of **9** was slightly lower (95.0:5.0) than the starting amide **8** (96.1:3.9), indicating a small amount of epimerization had occurred.[9]

Scheme 2. **Synthesis of (2*S*,3*S*)-2-ethyl-3-methylvaleramide (1)**



The original literature procedure used oxalyl chloride/DMF and NH_4OH to convert acid **9** to valeramide **1**.[4] Although the reaction was fast and clean, several processing issues were noticed at large scale, as well as concern about dimethylcarbamoyl chloride formation resulting from the presence of DMF.[10] Concentration in vacuo was required to remove the excess oxalyl chloride, causing loss of the volatile acyl chloride intermediate. Excess oxalyl chloride would react with ammonium hydroxide to form a white solid, presumably the corresponding oxamide, which was nearly insoluble in aqueous or organic solvents and complicated the workup.

There were several other challenges in developing a scaleable process to convert **9** to **1**. Valeramide **1** is poorly soluble in organic solvents so extractions would have required a large volume of any organic solvent. The physical properties of **1** are such that, once nucleation occurs during concentration, instantaneous crystallization ensues, trapping solvents. The complete removal of solvents at this point by concentration in vacuo was impractical for scale-up. A number of options were investigated, and finally an acceptable alternative process was developed in which **9** was added to neat thionyl chloride. The acyl chloride formation reaction was complete after 3 h at ambient temperature. The reaction solution was added to a

(7) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badia, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763.

(8) Efforts to efficiently form and convert **8b** directly to **1** were unsuccessful.

(9) A small-scale experiment showed that the pseudoephedrine auxiliary can be recovered from the hydrolysis mixture in ~75% yield by NaOH basification and CH_2Cl_2 extractive workup.

(10) Levin, D. *Org. Process Res. Dev.* **1997**, *1*, 182.

cooled NH_4OH aqueous solution. The resultant slurry was heated to 65 °C, and acetone was added until a clear solution was formed. The solution was cooled slowly to ambient temperature, and seeding was performed at 50 °C, after which the product crystallized. There was no detectable epimerization during this operation. This initial crystallization provided product that was slightly below our specification of 98% enantiomeric purity, and there remained a small amount of NH_4Cl in the product. An additional crystallization and polish filtration provided product with consistent chemical and optical purity. The solid was dissolved into hot EtOAc and washed with water to remove NH_4Cl. The organic solution was passed through a cartridge filter to remove fines and was concentrated to ~2 volumes. The API was crystallized by the addition of *n*-heptane followed by cooling ramp, while seeding at 60 °C. The isolated off-white crystalline product **1** was consistently >99.0% chemical purity and >98.5% enantiomeric purity over several multikilogram batches.

In summary, a concise stereoselective total synthesis of **1** was achieved by using (1*S*,2*S*)-pseudoephedrine as the chiral auxiliary. The overall yield of this eight-step synthesis was 41% with >99.0% chemical purity and >98.5% optical purity.

Experimental Section

All the reactions were performed under a positive pressure of nitrogen. Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded on a Varian Mercury 300 MHz.

(3*S*)-Methylvaleric Acid (6). To a suspension of L-isoleucine (5.00 kg, 38.12 mol) in water (12.25 L) at −5 °C was added 48% HBr (25.90 L) over 1 h to give a clear solution. The internal temperature rose to ~10 °C and was cooled to −5 °C before the slow addition of a sodium nitrite (5.26 kg, 76.24 mol, 2 equiv) solution in water (10.0 L) over 2 h, maintaining the reaction temperature at 0 ± 5 °C. The heavy, brown gas released from the reaction was scrubbed by 20% NaOH solution (40 L). The resultant mixture was warmed to ambient temperature and stirred for 4 h. This dark-red solution was extracted with MTBE (15 L × 3). The combined red organic extracts were washed with 3.0 M sodium bisulfite (15 L × 2), water (15 L), and brine (15 L) and concentrated in vacuo to afford bromo acid **5**.

The bromo acid **5** was dissolved in H_2SO_4 (2 M, 40 L) and cooled to 0 °C. Zinc powder (2.74 kg, 41.92 mol, 1.10 equiv) was added in portions, maintaining the reaction temperature <20 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was filtered and extracted with MTBE (25 L × 2). The combined organic extracts were washed with water (25 L) and brine (25 L) and concentrated in vacuo. The crude yellowish oil was purified by vacuum distillation (75−78 °C at 5 mmHg) to afford acid **6** as a colorless oil, 3.50 kg, 79% yield. GC−MS analysis indicated >99% purity with *m*/*z*: 87 (M − 29), 60 (M − 29 − 27). $[\alpha]^{20}_D$ = +5.5 (*c* = 1.0 in MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (dd, J_1= 15.0 Hz, J_2 = 6.0 Hz, 1H); 2.14 (dd, J_1 = 15.0 Hz, J_2 = 8.1 Hz, 1H); 1.92−1.85 (m, 1H); 1.45−1.35 (m, 1H); 1.34−1.20 (m, 1H); 0.97 (d, J = 3.9 Hz, 3H); 0.92 (t, J = 7.5 Hz, 3H). IR (film, cm^{-1}): 2964, 1708. Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.24; H, 10.38.

(*S*)-3-Methylpentanoic Acid, ((1′*S*,2′*S*)-2′-Hydroxy-1′-methyl-2′-phenylethyl)methyl-amide (7). To a solution of **6** (2.32 kg, 20.00 mol) in CH_2Cl_2 (14 L) at −5 °C was added Et_3N (2.93 L, 2.12 kg, 21.00 mol, 1.05 equiv), followed by pivaloyl chloride (2.46 L, 2.41 kg, 20.00 mol, 1.00 equiv), while maintaining the internal temperature <0 °C. The resultant slurry was stirred for 1 h, and then Et_3N (2.93 L, 2.12 kg, 21.00 mol, 1.05 equiv) was added. (1*S*,2*S*)-(+)-Pseudoephedrine (3.30 kg, 20.00 mol, 1.00 equiv) was added as a solid in portions, maintaining the internal temperature <5 °C. The resultant slurry was stirred for 1 h, and water (14 L) was added. The organic layer was isolated, washed with 1 M HCl (14 L), 1 M NaOH (14 L), and water (14 L) and concentrated in vacuo to constant residue weight. The residue was dissolved in THF (10 L) and concentrated in vacuo to constant residue weight again. The residue (amide **7**) was dissolved in THF (10 L) and used in the next step without any further purification or treatment. LC−MS indicated >99% purity with *m*/*z*: 264 (M + 1), 246 (M − 17). Chiral HPLC indicated >99.5% chiral purity. A sample was purified by flash chromatography (5% MeOH in CH_2Cl_2) for analytical characterization. $[\alpha]^{20}_D$ = +97.4 (*c* = 1.0 in MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.26 (m, 5H), 4.62−4.55 (m, 1H), 4.50−4.40 (m, 1H, with minor rotamer at 4.10−3.95 ppm), 2.81 (s, 3H, with minor rotamer at 2.91 ppm, 3.4:1), 2.29−2.10 (m, 2H), 2.00−1.80 (m, 1H), 1.37−1.32 (m, 2H), 1.22−1.11 (m, 3H), 1.00−0.86 (m, 6H). IR (film, cm^{-1}): 3377, 2961, 1620. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.69; H, 9.86; N, 5.12.

(2*R*,3*S*)-2-Ethyl-3-methylpentanoic Acid, ((1′*S*,2′*S*)-2′-Hydroxy-1′-methyl-2′-phenylethyl)methyl-amide (8). To a solution of anhydrous LiCl (1.70 g, 40.00 mol, 2.00 equiv) in THF (20 L) and diisopropylamine (6.45 L, 4.65 kg, 46.00 mol, 2.30 equiv) at −20 °C was added *n*-BuLi (18.40 L, 2.50 M in cyclohexane, 46.00 mol, 2.30 equiv) slowly while maintaining the internal temperature <−10 °C. After 30 min, a solution of amide **7** (20.00 mol) in THF (10 L) from the previous step was slowly added while maintaining the internal temperature <−10 °C. After 30 min, EtI (3.20 L, 6.24 kg, 40.00 mol, 2.00 equiv) was slowly added while maintaining the internal temperature <−10 °C. After 2 h, the reaction mixture was warmed to 20 °C and stirred overnight. Saturated NH_4Cl (20 L) was added to quench the reaction. The organic layer was separated and washed with water (20 L). The combined aqueous layers were extracted with MTBE (20 L), the layers were separated, and the MTBE layer was washed with water (20 L). The MTBE layer was combined with the original organic layer and concentrated to constant residue weight. The residue was dissolved in 1,4-dioxane (10 L) and concentrated to constant residue weight. The residue (amide **8**) was dissolved in 1,4-dioxane (10 L) and used in the next step without any further purification or treatment. LC−MS indicated >99% purity with *m*/*z*: 292 (M + 1), 274 (M − 17). Chiral GC indicated 96.1:3.9 diastereomeric purity. A sample was purified by flash chromatography (5% MeOH in CH_2Cl_2) for analytical characterization. $[\alpha]^{20}_D$ = +58.9 (*c* = 1.0 in MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.22 (m, 5H), 4.65−4.60 (m, 1H), 4.50−4.40 (m, 1H, with minor rotamer at 4.20−4.10 ppm), 2.87 (s, 3H, with minor rotamer at 2.91 ppm, 8.7:1), 2.40−2.17 (m,

1H), 1.68−1.52 (m, 5H), 1.19−1.09 (m, 3H), 1.08−0.82 (m, 6H), 0.74 (t, J = 7.5 Hz, 3 H). IR (film, cm^{-1}): 3383, 2965, 1616. Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.53; H, 10.38; N, 4.62.

(2*S*,3*S*)-2-Ethyl-3-methylvaleric Acid (9). To the amide **8** (20.00 mol) solution in 1,4-dioxane (10 L) from the last step was added 3 M H_2SO_4 (10 L, 30.00 mol, 1.50 equiv). The resultant mixture was refluxed (∼90 °C) for 6 h and then cooled to 80 °C. Concentrated H_2SO_4 (6.67 L, 18 M, 120 mol, 6.00 equiv) was added, and the mixture was refluxed (∼125 °C) for 16 h followed by cooling to 20 °C. The black mixture was extracted with *n*-heptane (20 L × 2). The combined organic layers were washed with water (10 L), cooled to 0 °C, and then extracted with 4 M NaOH (7.50 L × 2). The combined basic extracts were washed with *n*-heptane (10 L) and cooled to 0 °C. Concentrated HCl (8 L) was carefully added to provide an acidic solution (pH < 2) that was extracted with *n*-heptane (20 L × 2). The combined organic layers were washed with water (10 L), filtered, and concentrated in vacuo to constant residue weight to afford (2*S*,3*S*)-2-ethyl-3-methylvaleric acid **9** as a pale-yellow oil, 2.19 kg, 76% yield from (3*S*)-methylvaleric acid **6**. Acid **9** was used in the next step without any further purification or treatment. GC−MS indicated >99% purity with *m*/*z*: 115 (M − 29), 88 (M − 29 − 27). Chiral GC indicated 95.0:5.0 diastereomeric purity. $[\alpha]^{20}_D = +2.0$ (c = 1.0 in MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24−2.17 (m, 1H); 1.70−1.46 (m, 4H); 1.25−1.15 (m, 1H); 0.95−87 (m, 9H). IR (film, cm^{-1}): 2965, 2879, 1704. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.35; H, 11.45.

(2*S*,3*S*)-2-Ethyl-3-methylvaleramide (1). Acid **9** (2.10 kg, 14.56 mol) was slowly added to $SOCl_2$ (1.17 L, 1.91 kg, 16.05 mol, 1.10 equiv) at 20 °C (off-gassing occurs during this operation, which was scrubbed using a 20% NaOH solution). After stirring for 3 h, the resultant solution was slowly added to 28% NH_4OH (7.87 L, 7.09 kg, 116.61 mol, 8 equiv) at −20 °C while maintaining the internal temperature <0 °C. The resultant slurry was warmed to 20 °C and stirred for 1 h. The slurry was heated to 65 °C, and acetone (5.85 L) was added to give a clear solution. Water (8.75 L) was added over 30 min while maintaining the internal temperature >60 °C. The resultant clear solution was cooled to 50 °C, and seed crystals (2 g) were added. The resultant slurry was cooled to 0 °C over 12 h. The solid was collected by filtration and washed with H_2O (4.38 L × 2) and *n*-heptane (4.38 L × 2). The product wet cake was dissolved in EtOAc (15 L) at 50 °C, washed with water (5 L), and filtered through a 0.3 μm filter. Approximately 12 L of EtOAc was removed by distillation at atmospheric pressure. *n*-Heptane (15 L) was slowly added to this hot EtOAc solution while maintaining the internal temperature >75 °C. The resultant clear solution was cooled to 60 °C, seed crystals (2 g) were added, and the slurry was cooled to 0 °C over 12 h. The solid was isolated by filtration, washed with *n*-heptane (3 L × 2), and dried at 50 °C under vacuum overnight to give (2*S*,3*S*)-2-ethyl-3-methylvaleramide **1** as a white crystalline solid, 1.42 kg, 68% yield. GC−MS analysis indicated greater than 99% purity with *m*/*z*: 114 (M − 29), 87 (M − 29 − 27). Chiral GC indicated 99.36% (2*S*,3*S*), 0.38% (2*R*,3*S*) and 0.26% (2*S*,3*R*) isomers. Mp (DSC): 131.5 °C. $[\alpha]^{20}_D = -12.1$ (c = 1.0 in MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.53 (s, 1H); 5.39 (s, 1H); 1.89−1.84 (m, 1H); 1.64−1.47 (m, 4H); 1.25−1.10 (m, 1H); 1.00−0.86 (m, 9H). IR (KBr, cm^{-1}): 3381, 3198, 2968, 1652. Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.35; H, 12.06; N, 9.82.

Acknowledgment

We are grateful to Dianna Cregg, and Raymond Dagnino for assistance with raw material sourcing. Louise Bernier, Elina Kolosovsky-Simberg, Laura Kuhn, Nate Martinez, Kevin Schaab, and Arthur Shurtleff are thanked for timely analytical method development and product analyses.

Supporting Information Available

Detailed analytical methods (HPLC−MS, chiral HPLC, GC−MS and GC-FID) and spectral data for compounds **1**, **6**, **7**, **8**, **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review October 9, 2008.

OP800260J