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The efficient synthesis of (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid, a chiral β-amino acid with potent affinity for the $\alpha_2\delta$ protein

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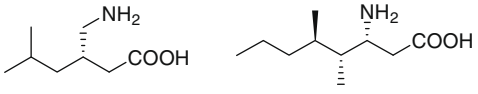
ABSTRACT

A chiral β-amino acid containing three contiguous chiral centers was synthesized efficiently in 11 steps, employing enantio-enriched β-ketoester as a key intermediate, via stereoselective catalytic hydrogenation of the corresponding enamide. Stereoselective 1,4-addition of a methyl group and protonation were key to the preparation of the desired acid **12**. Mild and efficient reaction conditions were applied to the enamine formation and protection to avoid epimerization at C-4 of compounds **13** and **14**. The final compound was found to display potent affinity for the $\alpha_2\delta$-protein that is a recognized drug target for the treatment of a variety of diseases.

The synthesis of chiral amino acids consistently attracts strong interest from across the synthetic organic chemistry community.[1] In addition to being attractive synthetic targets, amino acids often have profound biological activity.[2]

Pregabalin (Lyrica®),[3] a chiral γ-amino acid,[4] is approved in the US for the treatment of post-herpetic neuralgia and as an add-on therapy for epilepsy. With additional approval in the EU for generalized anxiety, pregabalin is emerging as a key medicine available to physicians, and has attracted much interest due to its therapeutic properties, pharmacology, and structure–activity relationships. With respect to the latter, we undertook the synthesis and biological evaluation of β-amino acid analogues of pregabalin.[5] Herein, we report an efficient preparation of the synthetically challenging β-amino acid (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid using a chiral β-ketoester as the key intermediate (Fig. 1).

The target amino acid **2** is notably more complex and poses a greater synthetic challenge than γ-amino acid **1**. It was important to develop a robust synthetic route to allow preparation of sufficient material to support pre-clinical studies. The original route to the targeted amino acid (Scheme 1) was based on the key intermediate chiral aldehyde **7**, which was prepared from crotonic acid via oxazolidinone chemistry.[6] Asymmetric conjugate addition of organocopper reagent, prepared from *n*-propylmagnesium chloride and CuBr.SMe, to oxazolidinone **4**,[7] followed by treatment with excess MeI (5 equiv) resulted in a diastereomeric mixture which was extremely difficult to purify. Reduction of oxazolidinone **5** with $LiAlH_4$, followed by PCC oxidation gave chiral aldehyde **7**. The subsequent chemistry involved the use of Davis' (***S***)-*p*-toluenesulfinamide[8] to transform **7** into chiral imine **8**, followed by stereoselective Ti (IV)-mediated Reformatsky-type reaction to obtain **9**. There were several issues with this approach: (1) The reaction of **4** to **5** resulted in a 3:1 to 5:1 diastereomeric mixture and



1, Pregabalin **2**

Figure 1. Structure of pregabalin **1** and (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid **2**.

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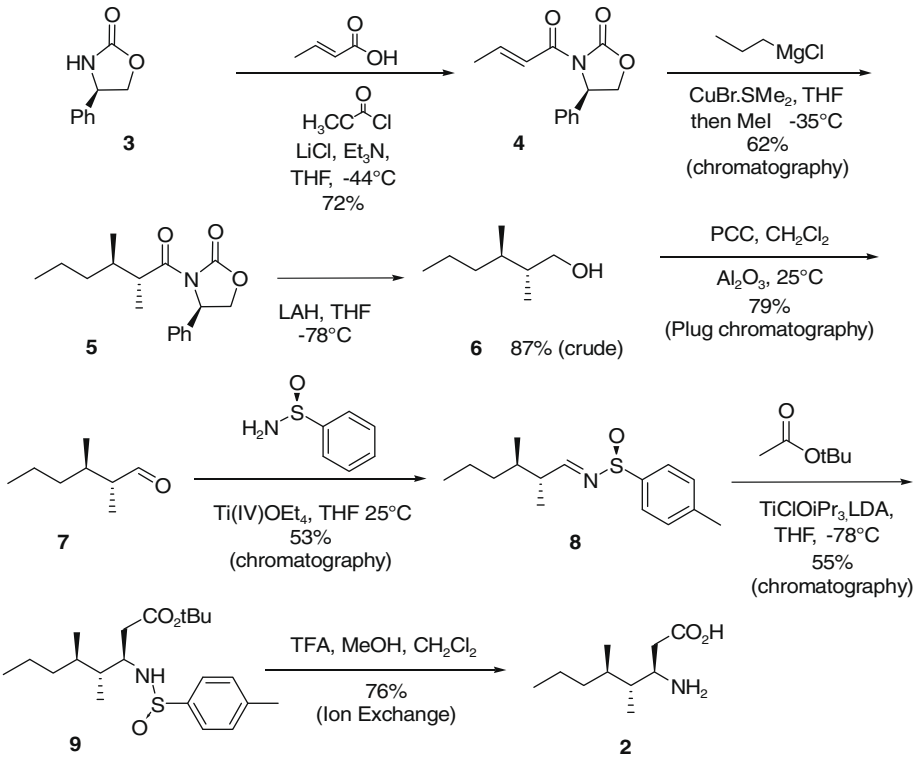


Scheme 1. Original route to enriched (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid **2** from chiral aldehyde **7**.

the crude material was an oil, requiring a tedious isolation and purification to enrich **5**; (2) oxidation of **6** to **7** utilized scale-unfriendly PCC, and provided a product prone to racemization; (3) conversion of **7** to **8** and **8** to **9** consistently afforded low yields (53% and 55%); (4) ion exchange chromatography used to isolate and purify final product required large volumes of NH_4OH and aqueous HCl. Poor product recovery was compounded by the difficulty of removing water as scale increased; (5) isomeric impurities in the final isolated product were persistent, and upgrading was extremely difficult.

The original route was modified as follows (Scheme 1): First, chiral aldehyde **7** was prepared from **5** by thioester formation followed by Fukuyama reduction (Pd/Et_3SiH),[9] avoiding $LiAlH_4$ reduction and PCC oxidation. Conversion of **8** to **9** was improved to >90% yield and the need for chromatographic purification was eliminated, and instead of deprotection using TFA/MeOH, followed by ion exchange chromatography, the HCl salt of (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid was prepared directly. Recrystallization from MeOH/MeCN effectively removed isomeric impurities. Using this route, >10 g of enriched (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid was delivered (both chemical and chiral purity >99%). But despite the improvements in the orginal route, chiral aldehyde **7** was found to be an unstable intermediate, highly volatile, and prone to epimerization. In addition, intermediates **7**, **8**, **9,** and **2** are oils, offering no opportunity for facile purification on scale. With the realization that aldehyde **7** was not a viable intermediate for further scaling, an alternative, chiral acid **12** was identified as a key intermediate in the preparation of β-ketoester **13**, itself a precursor for a stereoselective enamide hydrogenation, and a new approach was designed as illustrated (see Supplementary data).

To confirm the viability of a β-ketoester as an intermediate in the synthesis of (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid **2**, and to prepare a racemic standard to help identify and assign absolute stereochemistry to the impurities in the final product, we decided to test the β-ketoester route utilizing a mixture of acid isomers of **12**. This route started with an indium triflate-mediated addition of ethyl methylmalonate to 1-pentyne. Subsequent reduction, saponification, and decarboxylation gave racemic acid **12**.[10] (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid, and all possible stereoisomers (Fig. 2) were synthesized in eight steps, in good yield, via the β-ketoester isomer mixture (see Supplementary

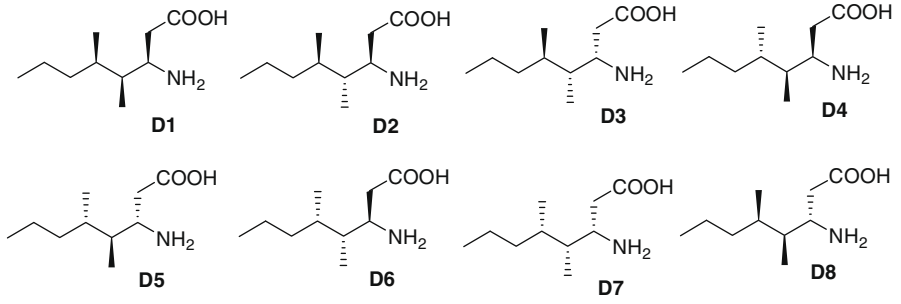
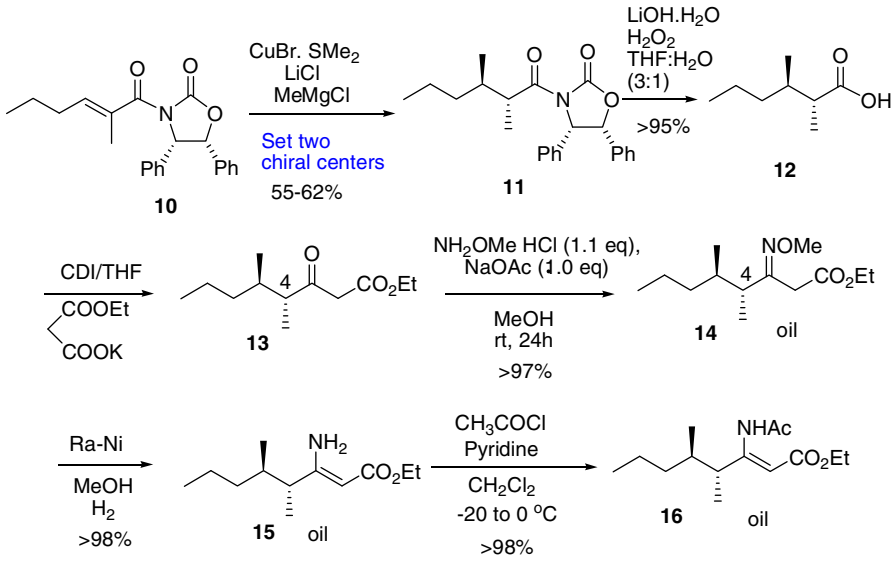


Figure 2. All possible stereoisomers of 3-amino-4,5-dimethyl-octanoic acid.



Scheme 2. Mild and efficient method to prepare chiral enamine.

data). Thus, this indicated that a new route based on a chiral β-ketoester was chemically feasible, and we therefore turned our attention to the preparation of enantiomerically pure acid **12**.

Enantio-enriched acid **12** was prepared from intermediate **5** by $LiOH/H_2O_2$ hydrolysis to remove the chiral auxiliary. Following the approach described (see Supplementary data), the corresponding enamide **16** was synthesized in two operations. Raney-Ni-catalyzed hydrogenation of the enamide, followed by HCl hydrolysis, afforded a mixture of desired product and its diastereomer in a ratio of 2.7:1 (or 64%:24% at the β-position). This early encouraging result from the Ra-Ni reduction suggested that a thorough screening of hydrogenation catalysts and reaction conditions was necessary.

The early reaction conditions[11] ($MeOH/NH_4OAc$ in rt for four days, then acetic anhydride/pyridine at 110 °C for 16 h) to form enamide **16** caused epimerization at the C-4 position and resulted in low yield of the desired product. We considered that firstly, the enamine formation gave low conversion due to the poor reactivity of NH_4OAc and steric hindrance of neighboring chiral center. Secondly, in the subsequent step, the harsh condition (with base at elevated temperature) to make enamide **16** caused epimerization. Thus, a mild and efficient method to prepare chiral enamide **16** became our main focus.

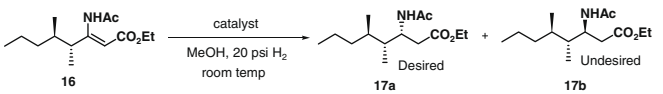
Several reagents, such as NH_2NHPh, NH_2OH, NH_2NH_2, and $BnNH_2$, were studied for the enamine formation, but none provided a single product in high yield under mild conditions. Since the above reagents have more than one reactive site, we turned our attention to $NH_2OMe{\cdot}HCl$ (Scheme 2). Indeed the combined reagent system (1.1 equiv $NH_2OMe{\cdot}HCl$ with 1.0 equiv NaOAc) in MeOH not only gave almost quantitative conversion in 24 h at rt, but also simplified the work-up. Intermediate **14** was isolated in 98% yield by removing MeOH after filtration. Without further purification, the N–O bond **14** was hydrogenated with Ra-Ni giving **15** in excellent yield (98%). Protection with acetyl chloride/pyridine at −20 to 0 °C also turned out to be very successful (yield >98%). The beauty of these three steps is that while each product is a liquid, due to the excellent yield, mild conditions, and high purity for each step, crude material could be carried forward in the next transformation without further purification. Moreover, epimerization at C-4 was significantly minimized due to the mild reaction conditions (ratio of desired:undesired >20:1 at the γ-position).

With pure enamide **16** in hand (>95% *Z*), a screen was conducted to determine the best reaction conditions for catalytic hydrogenation. After screening (Table 1), the optimal conditions were implemented in a successful scale-up employing crude **13**. In this case, we achieved excellent conversion (>98%) with acceptable selectivity (entry 5, in small scale: dr = 97:3, in larger scale, dr = 92:8).

With the *Z*-enamide as the reactant, we believe that a hydrogen bond between the NH and the carbonyl oxygen exists, thus a Cram-chelation model is best to explain the stereochemical outcome (Scheme 3). It was reported that hydrogenation of δ-hydroxy-β-ketoester preferentially gave *syn*-1,3-diols with high diastereoselectivity.[12] Prasad and co-workers suggested that the formation of an intramolecular hydrogen bond explains this stereochemical outcome. Recently, Ma reported the preparation of *syn*-δ-hydroxy-β-amino ester via hydrogenation of δ-hydroxy-β-ketoester-derived enamine with high diastereoselectivity.[13] To rationalize the result, intramolecular hydrogen bonds between the δ-hydroxyl group and the nitrogen atom were invoked. In our own case, without the hydrogen bonding we believe that the neighboring group (CH_3) plays an important additive role in controlling facial selectivity of the addition of hydrogen to provide (3*R*,4*R*,5*R*)-3-acetylamino-4,5-dimethyl-octanoic acid.

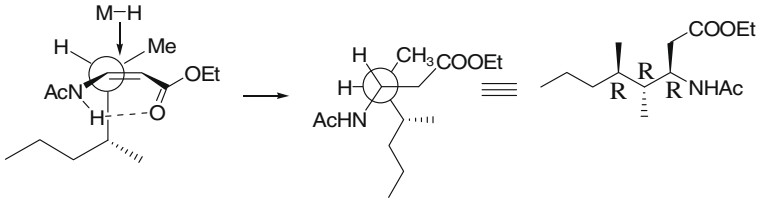
Since (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid is a chiral β-amino acid with three contiguous chiral centers, the isomeric impurity or quality control was critical. Similar physicochemical properties of stereoisomers (Fig. 2) made separation of one from an-

Table 1
Hydrogenation screening



Entry	Catalyst	Conversion (%)	**17a**:**17b**[a]
1	5% $Pd/SrCO_3$	66	52:1
2	5% Pd/MgO	93	38:1
3	5% $Pd/CaCO_3$	99	34:1
4	5% $Pd/CaCO_3$	89	33:1
5	5% $Pd/BaSO_4$	100	31:1
6	5% Pd/Al_2O_3	100	28:1
7	5% $Pd/BaSO_4$	100	20:1
8	5% $Pd/BaCO_3$	100	17:1

[a] Measured by chiral GC.



Scheme 3. Cram-chelation model for hydrogenation of chiral enamide **16**.

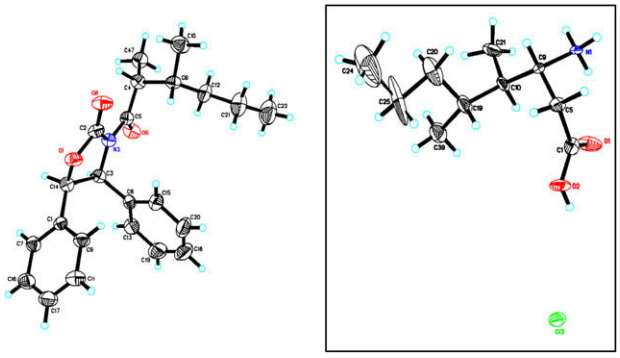


Figure 3. X-ray crystal structure of intermediate **11**, and HCl salt of (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid **2**.

other a daunting task. We had to identify the isomeric impurities in our final product, and determine their origin and the maximum tolerable level. A careful study indicated that removal of isomeric impurity D7, which arises from poor selectivity in the 1,4-Michael addition, would be difficult. Impurity D3 was always present because the catalytic hydrogenation was not 100% selective; fortunately, D3 was the most easily removed impurity by recrystallization.

In the final optimization of the synthesis, (1*R*,2*S*)- diphenyl-2-oxazolidinone was used as chiral auxiliary to provide intermediates with better crystallinity **11** (Fig. 3, X-ray crystal structure). EEDQ[14] (*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline), a convenient and efficient reagent for peptide synthesis, was used for the coupling of commercially available 2-methyl-2-pentenoic acid with diphenyl-2-oxazolidinone to provide **10**. Addition of MeMgCl and quenching of the enolate with acetic acid gave predominantly **11** which, after recrystallization, provided enriched **11** in 55–62% yield and 93% diastereomeric purity and avoided the use of MeI.[15] This material could be further purified by recrystallization (95:5 = heptane/toluene) to give **11** having >98% chemical and chiral purity.

In conclusion, a potent $\alpha_2\delta$ ligand,[16] chiral β-amino acid with three contiguous chiral centers was synthesized efficiently over 11 steps using chiral β-ketoester **13** as a key intermediate. Epimerization at C-4 was minimized. Early process chemistry has been developed which is free of chromatography and produced >300 g of (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid **2** having excellent chemical (>99%) and chiral (99%) purity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.111.

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16. Amino acid **2** was found to display an IC50 of 24 nM for the $\alpha_2\delta$-1 protein and 123 nM for the $\alpha_2\delta$-2 protein.