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Diastereoselective, large-scale synthesis of β-amino acids via asymmetric *aza*-Michael addition as α2δ ligands for the treatment of generalized anxiety disorder and insomnia

Javier Magano [a,*], Daniel Bowles [a], Brian Conway [a], Thomas N. Nanninga [b], Derick D. Winkle [c]

[a] *Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340, USA*
[b] *Bridge Organics, 311 W Washington, Vicksburg, MI 49097, USA*
[c] *Pleotint LLC, 7705 West Olive Road, West Olive, MI 49460, USA*

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ABSTRACT

Scalable synthetic routes to β-amino acids **1** and **2** are presented. These two compounds, which bind to the α2δ subunit of calcium channels and have important medical applications, have been prepared on kilogram scale in our pilot plant through an improved synthesis that avoids the use of highly toxic reagents and hazardous chemistry present in the original Medicinal Chemistry route. The two chiral centers are introduced through asymmetric Michael and *aza*-Michael reactions with excellent diastereoselectivity.

α2δ-Ligands are compounds that selectively displace ^{3}H-gabapentin from brain membranes, indicating a high affinity interaction with the α2δ subunit of voltage-gated calcium channels.[1] This type of compound can be used to treat a number of conditions such as generalized anxiety disorder (GAD), insomnia, fibromyalgia, epilepsy, neuropatic pain, anxiety, depression, and attention hyperactivity disorder, among others.[2] Recently, we have been interested in the synthesis of compounds **1** and **2** as candidates for the treatment of generalized anxiety disorder and insomnia, respectively. With the goal of preparing large quantities of these materials for clinical trials, we have developed two different and efficient approaches: the 'Michael addition route', described in this Letter, and the 'Enamide hydrogenation route' described in the following article.

The medicinal chemistry route for the preparation of these compounds is shown in Scheme 1.[3] The synthesis started with (*R*)-β-citronellol (**3**), which already possesses one of the chiral centers of the target molecule in the desired configuration. Mesylation under standard conditions followed by displacement of the leaving group in **4** with either methyl or ethylmagnesium bromide in the presence of LiCl and CuCl provided alkenes **5** and **6**, respectively.[4] The double bond was then oxidized with Jones reagent to give acids **7** and **8**.[5] The rest of the synthesis is illustrated through the use of acid **7** as a representative example. Thus, **7** underwent reaction with pivaloyl chloride (**9**) in the presence of Et_3N to give mixed anhydride **10**, which was treated with oxazolidinone **11** to generate intermediate **12**.[6] The deprotonation of **12** with NaHMDS followed by the addition of *tert*-butyl bromoacetate afforded *tert*-butyl ester **13** in good yield and excellent diastereoselectivity.[7] The cleavage of the oxazolidinone with LiOH and H_2O_2 gave acid **14** as a yellow viscous oil,[8] which was used directly in the next step. At this point, the chiral auxiliary could be recovered in nearly quantitative yield. The key Curtius rearrangement was accomplished by heating acid **14** with diphenylphosphoryl azide (DPPA)[9] and triethylamine in *tert*-butyl methyl ether at 45 °C to give crude isocyanate **15**, which was immediately treated with 6 N HCl at reflux to afford β-amino acid **1** as its HCl salt. Homologue **2** was prepared in a similar fashion from carboxylic acid **8**.

This route proved satisfactory to provide small amounts of material for preliminary studies but several issues were identified that did not make it amenable for scale up, such as the cost of (*R*)-β-citronellol, the highly toxic waste generated by the Jones oxidation, and the use of hydrogen peroxide and DPPA, both of which are

* Corresponding author. Tel.: +1 860 6869021.
E-mail addresses: Javier.Magano@Pfizer.com, jmaganop@yahoo.com (J. Magano).

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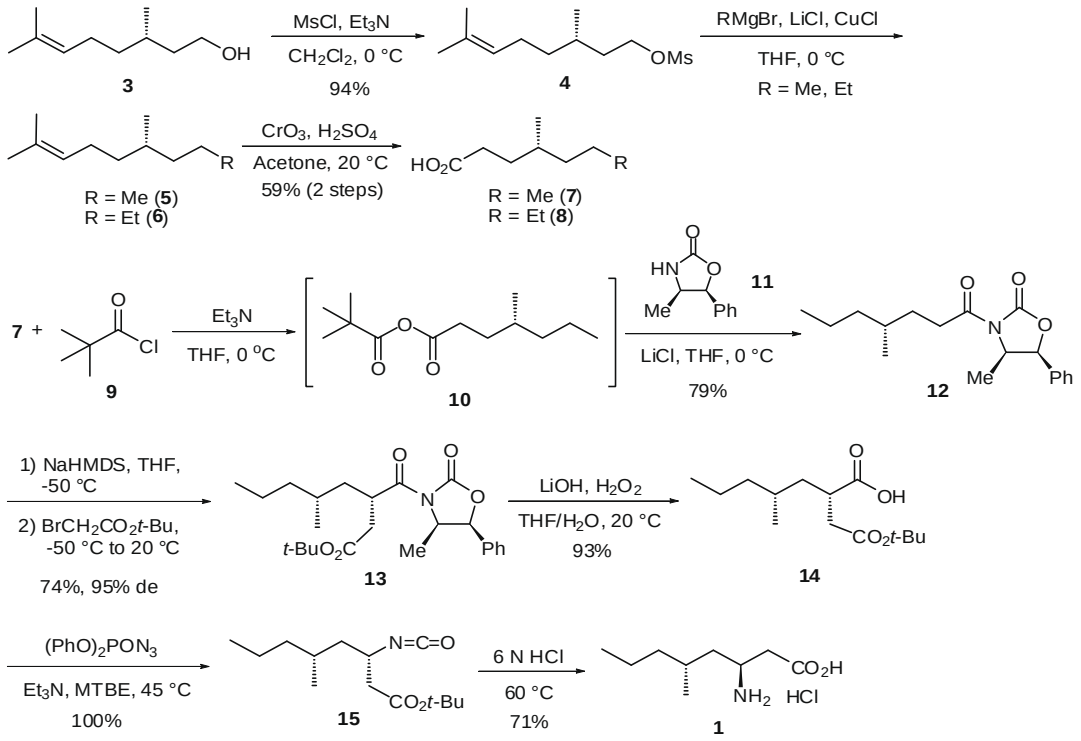
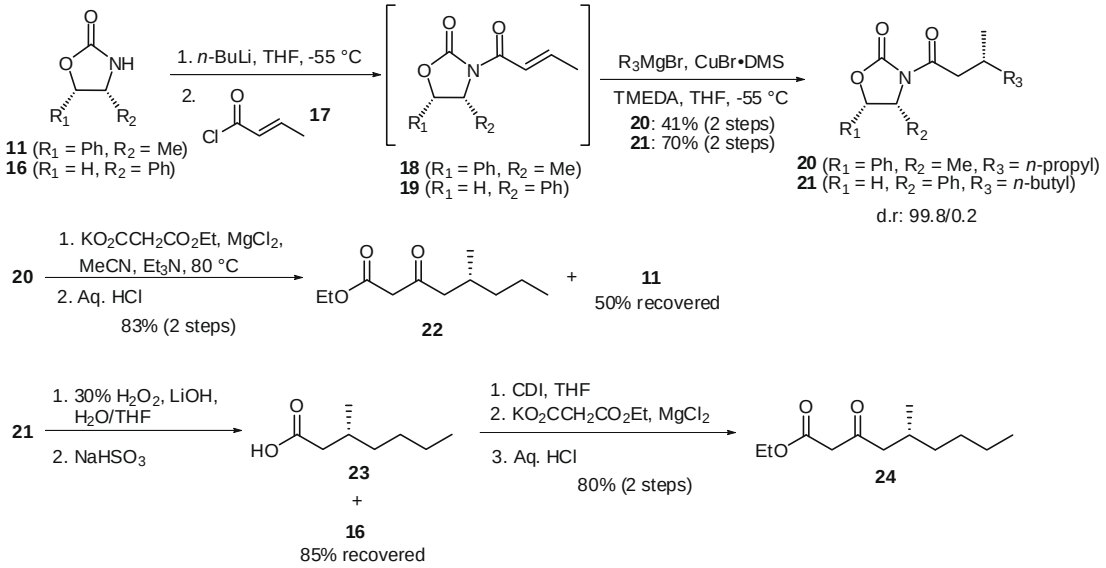
hazardous reagents. As a result of these limitations, we developed an alternate route toward **1** and **2** that circumvented these problems and enabled a more process-friendly synthesis. Even though this new route is essentially the same for both **1** and **2**, it employs different chiral auxiliaries for each substrate as well as alternative protocols for the removal of the auxiliary to produce an intermediate β-ketoester.

The preparation of β-ketoesters **22** and **24** is described in Scheme 2. Oxazolidinones **11** and **16**, derived from (1*S*,2*R*)-(+)-norephedrine and L-(+)-α-phenylglycine, respectively, were deprotonated with *n*-BuLi followed by acylation with crotonyl chloride (**17**) to afford intermediates **18** and **19**.[10] This direct method was preferred to the mixed anhydride methodology described in the original synthesis (Scheme 1), since it is operationally simpler and generates a much smaller amount of waste. Without isolation, *N*-acyl oxazolidinones **18** and **19** were treated with the cuprates derived from *n*-propyl and *n*-butylmagnesium bromide, respectively, and CuBr·Me_2S to give Michael addition products **20** and **21** in excellent diastereoselectivity after recrystallization from hexane.[11] Although the level of conversion was not affected, the level of enantioselectivity was improved by utilizing multiple equivalents of the cuprate reagent (97% ee using 3.1 equiv vs 92% ee



Scheme 1. Medicinal chemistry route for the preparation of α2δ ligands **1** and **2**.



Scheme 2. Scalable syntheses of β-ketoesters **22** and **24** en route to α2δ ligands **1** and **2**.

using 1.6 equiv). Running the reaction at higher concentration also improved the selectivity but extremely thick slurries were obtained.

Different conditions were employed for the removal of the chiral auxiliaries. Thus, the oxazolidinone moiety in **21** was cleaved via the original oxidative protocol with H_2O_2 and LiOH[12] to give acid **23** which, after activation with 1,1′-carbonyldiimidazole, underwent reaction with potassium ethyl malonate (KEM) in the presence of $MgCl_2$ to afford β-keto ester **24**. Alternatively, the direct displacement of the chiral auxiliary in **20** was carried out in one step with KEM and $MgCl_2$ to provide β-keto ester **22** in similar yield. This methodology, which was developed in our laboratories,[13] considerably simplifies this transformation with respect to the traditional approach. At this point, the chiral auxiliaries **11** and **16** could be recovered in fair and good yield, respectively, even though this aspect of the synthesis was not optimized. Prior to the hydrogenation step, the purity of keto esters **22** and **24** was upgraded via treatment with Darco G-60 in ethanol at 50 °C for 3 h.

With β-keto esters **22** and **24** in hand, the reduction of the keto group was then investigated (Scheme 3). Several hydrogenation screens were completed in an Argonaut Endeavor Parallel Reactor using $(Ph_3P)_3RuCl_2$ as a catalyst[14] to determine the influence of pressure, temperature, catalyst loading, concentration, and the choice of acid on the process. The data showed that catalyst loading and temperature had the biggest impact on the reaction rate, while pressure had a lesser influence on the outcome. Also, H_2SO_4 was shown to be a viable alternative to HCl since this transformation had to be carried out in stainless steel equipment. The most effective conditions that emerged from the screen were 0.13 mol % of both Ru catalyst and H_2SO_4 under 50 psi of hydrogen in ethanol at 60 °C, which gave alcohols **25** and **26** in excellent yield. The $NaBH_4$ reduction in methanol was also investigated, but the product was contaminated with boron by-products, which made the purification difficult.

Subsequent mesylate formation and elimination in the presence of Et_3N gave α,β-unsaturated esters **27** and **28**. This transformation was originally carried out in acetonitrile, but ethyl acetate proved a greener alternative. In addition, it allowed for a more straightforward work-up after aqueous quench since, when acetonitrile was employed, it was necessary to distill most of the solvent to obtain good phase separation.

One of the key steps in this route is the introduction of the second chiral center. Based on the work of Davies et al.,[15] chiral amine **29** was first deprotonated with *n*-BuLi at −65 °C and the resulting anion was added to acrylates **27** and **28** to afford β-amino esters **30** and **31**, respectively, in excellent yield and diastereoselectivity. Good conversion was obtained using 1.3 equiv of amine **29**. In addition, quenching the reaction with dilute HCl gave a cleaner product profile in comparison with concentrated HCl or acetic acid. The debenzylation of intermediates **30** and **31** was carried out with palladium hydroxide on carbon and acetic acid as co-catalyst to accelerate the rate of reaction. Unfortunately, a heavy loading of the Pd catalyst (1 g/2.5 g of substrate) was found to be necessary to push the reaction to completion and to prevent the isolation of partially debenzylated intermediates. Finally, the ester group was hydrolyzed in hot, concentrated HCl to afford crudes **1** and **2**. After an extensive solvent screen, it was found that crystallization from the acid reaction mixture was most effective in affording the desired β-amino acids **1** and **2** in 66% and 40% yield, respectively, and de ⩾99%, with residual Pd and Rh contents below our specification of ⩽20 ppm. In addition, it was found that slow cooling helped reduce the amount of the major impurity identified as the (3*R*,5*R*)-diastereoisomer. The influence of the crystallization temperature in the diastereomeric purity and the yield of **2** is shown in Figure 1. Compounds **1** and **2** can be further recrystallized from 2-propanol to upgrade the optical purity to ⩾99.8% de.

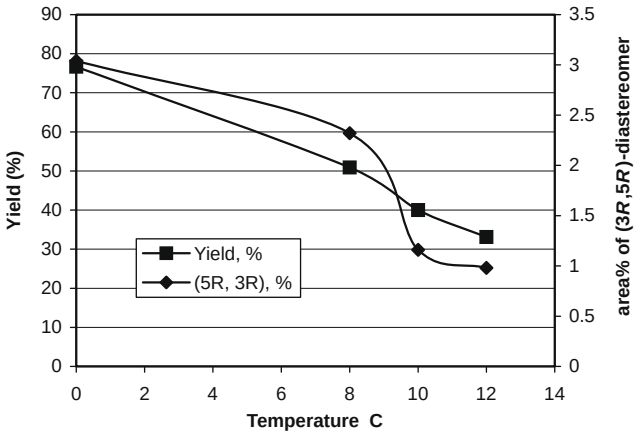


Figure 1. Diastereomeric purity and yield of **2** as a function of the crystallization temperature.

In conclusion, a scalable route for the preparation of α2δ ligands **1** and **2**[16] has been described that avoids the limitations encountered in the original synthesis. The feasibility of this technology has been demonstrated in our pilot plant on multi-kilogram scale, making possible the timely advance of associated drug development programs.

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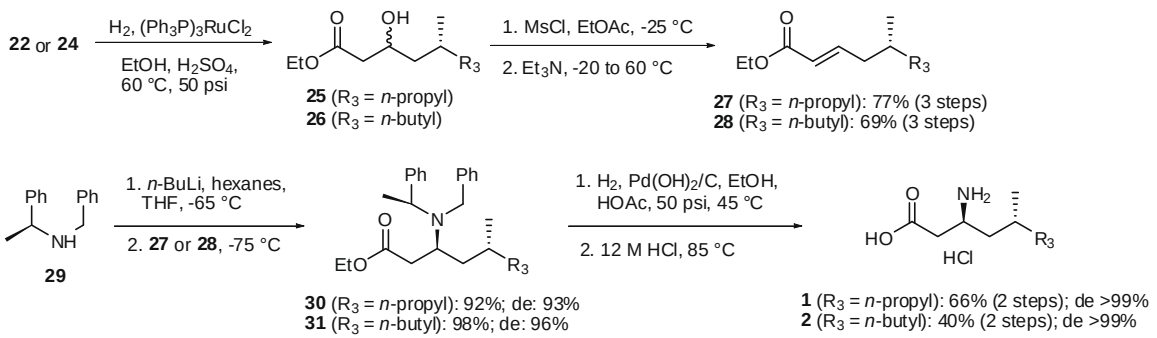

Scheme 3. Scalable synthesis for the preparation of α2δ ligands **1** and **2**. Completion of the synthesis.

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16. *Analytical data for* **1**: ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.93–1.00 (m, 6H), 1.17–1.26 (m, 1H), 1.32–1.52 (m, 4H), 1.61–1.77 (m, 2H), 2.63–2.78 (m, 2H), 3.61–3.68 (m, 1H), 4.99 (br s, 3H). ^{13}C NMR (100 MHz, methanol-d_4) δ ppm 13.47, 18.42, 19.67, 28.69, 36.55, 39.08, 40.14, 46.65, 172.44. MS (APCI+): *m/z* 174 (M+H). Anal. Calcd for $C_9H_{19}NO_2$·HCl: C, 51.54; H, 9.61; N, 6.68. Found: C, 51.91; H, 9.41; N, 6.80. $[\alpha]_D^{22}$ (14.35, *c* 0.64, MeOH).
Analytical data for **2**: ^{1}H NMR (methanol-d_4) δ ppm 0.90–1.03 (m, 6H), 1.17–1.47 (m, 7H), 1.56–1.72 (m, 2H), 2.23–2.42 (m, 1H), 2.42–2.59 (m, 1H), 3.38–3.58 (m, 1H), 5.13 (bs, 3H). ^{13}C NMR (methanol-d_4) δ ppm 13.33, 18.76, 22.84, 28.91, 28.94, 36.42, 38.78, 40.58, 47.68, 176.83. MS (APCI+): *m/z* 188 (M+H). Anal. Calcd for $C_{10}H_{21}NO_2$·HCl: C, 53.68; H, 9.91; N, 6.26. Found: C, 53.30; H, 9.69; N, 6.23. $[\alpha]_D^{22}$ (30.73, *c* 1.0, MeOH).