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Asymmetric Synthesis of Telcagepant, a CGRP Receptor Antagonist for the Treatment of Migraine

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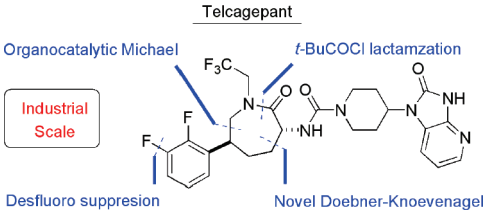

A highly efficient, asymmetric synthesis of telcagepant (**1**), a CGRP receptor antagonist for the treatment of migraine, is described. This synthesis features the first application of iminium organocatalysis on an industrial scale. The key to the success of this organocatalytic transformation was the identification of a dual acid cocatalyst system, which allowed striking a balance of the reaction efficiency and product stability effectively. As such, via an iminium species, the necessnary C-6 stereogenicity was practically established in one operation in >95% ee. Furthermore, we enlisted an unprecedented Doebner−Knoevenagel coupling, which was also via an iminium species, to efficiently construct the C3−C4 bond with desired functionality. In order to prepare telcagepant (**1**) in high quality, a practical new protocol was discovered to suppress the formation of desfluoro impurities formed under hydrogenation conditions to <0.2%. An efficient lactamization facilitated by *t*-BuCOCl followed by a dynamic epimerization−crystallization resulted in the isolation of caprolactam acetamide with the desired C3 (*R*) and C6 (*S*) configuration cleanly. Isolating only three intermediates, the overall yield of this cost-effective synthesis was up to 27%. This environmentally responsible synthesis contains all of the elements required for a manufacturing process and prepares telcagepant (**1**) with the high quality required for pharmaceutical use.

Introduction

Migraine is a neurovascular disorder characterized by severe, debilitating, and throbbing unilateral headache.[1] Though a leading cause of disability, it is a highly prevalent disease with a clear unmet medical need.[1] With the significant progress achieved in the field of pathophysiology in the past decades, to date, it is well recognized that the neuropeptide calcitonin gene-related peptide (CGRP), which is expressed mainly in the central and peripheral nervous system, plays a crucial role in migraine.[2] Antagonism of CGRP receptors, as a potential new therapy for the treatment of migraine, could offer the advantage of avoiding the cardiovascular liabilities associated with other existing antimigraine therapies.[3,4] Indeed, telcagepant (**1**, Scheme 1),[5] a

(1) (a) Goadsby, P. J.; Lipton, R. B.; Ferrari, M. D. *N. Engl. J. Med.* **2002**, *346*, 257. (b) Stovner, L.; Hagen, K.; Jensen, R.; Katsarava, Z; Lipton, R.; Scher, A.; Steiner, T.; Zwart, J.-A. *Cephalalgia* **2007**, *27*, 193.

(2) For lead references, see: (a) Durham, P. L. *Headache* **2006**, *46* (suppl 1), S3. (b) Goadsby, P. J. *Drugs* **2005**, *65*, 2557. (c) Edvinsson, L. *Cephalalgia* **2004**, *24*, 611.

(3) For reviews, see: (a) Poyner, D. R.; Hay, D. L.; Conner, A. C. *Expert Opin. Drug Discovery* **2009**, *4*, 1253. (b) Villalón, C. M.; Olesen, J. *Pharmacol. Ther.* **2009**, *124*, 309.

(4) For lead references, see: (a) Lynch, J. J., Jr.; Regan, C. P.; Edvinsson, L.; Hargreaves, R. J.; Kane, S. A. *J. Cardiovasc. Pharmacol.* **2010**, *55*, 518. (b) Petersen, K. A.; Birk, S.; Lassen, L. H.; Kruuse, C.; Jonassen, O.; Lesko, L.; Olesen, J. *Cephalalgia* **2005**, *25*, 139. (c) Durham, P. L.; Russo, A. F. *Pharmacol. Ther.* **2002**, *94*, 77 and references therein.

(5) Paone, D. V.; Shaw, A. W.; Nguyen, D. N.; Burgey, C. S.; Deng, J. Z.; Kane, S. A.; Koblan, K. S.; Salvatore, C. A.; Mosser, S. D.; Johnston, V. K.; Wong, B. K.; Miller-Stein, C. M.; Hershey, J. C.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *J. Med. Chem.* **2007**, *50*, 5564.

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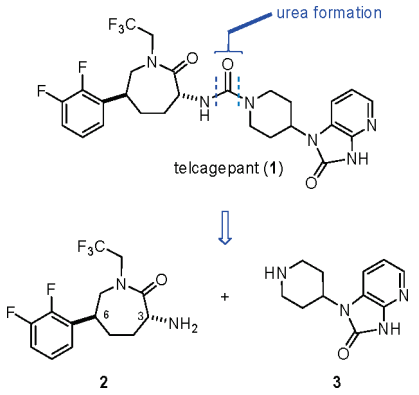
SCHEME 1. Retrosynthetic Analysis of Telcagepant (1)



selective and potent CGRP receptor antagonist, was recently demonstrated to be effective as an acute treatment for migraine in phase III clinical trials.[6]

Retrosynthetic disconnection of telcagepant (**1**) leads to two heterocyclic species, caprolactam **2** and piperidine **3**. As a practical synthesis of piperidine **3**[7] was realized recently, the key challenges to synthesize **1**, in particular, became two practical strategic aspects: (1) asymmetric setup of the C-3 and C-6 stereogenic centers in **2** and (2) effective construction of the caprolactam moiety with desired functionalities. To support the development of telcagepant, several syntheses of **2** have been realized.[5,8,9] Scheme 2 depicts the first generation of synthesis suitable for large scale preparation.[9]

In line with an early synthetic approach,[8a] the above successful synthesis also relies on a diastereoselective hydrogenation of dehydrocaprolactam to establish the C-6 stereogenic center in the caprolactam ring. After careful evaluation of the substrate of choice, a dramatic improvement in diastereoselectivity was achieved by hydrogenating dehydrocaprolactam **9** in the presence of Pd-$BaSO_4$. However, the hydrogenation gave a 13:1 mixture of *cis*/*trans* isomers in favor of the undesired *cis* isomer **10**. Fortunately, epimerization of the C-3 amino group of **10** could be achieved via an epimerizable imine intermediate by treating **10** with a catalytic amount of aldehyde **8** so that the desired *trans* isomer **2** could be obtained. To access the optimal hydrogenation substrate **9**, a racemic synthesis of **6** was achieved via Pd(0)-catalyzed epoxide opening of **4**[10] with acetamidomanolate **5**. The racemic substrate **7** was smoothly converted to the desired chiral dehydrocaprolactam **9** as its ditoluoyl L-tartaric acid salt via dynamic kinetic resolution (DKR)[11] crystallization in the presence of a catalytic amount of **8**.

This route provided a means to prepare large quantities (> 500 kg) of talcagepant to support the early safety and clinical studies. Despite the significant improvement over the early syntheses, the overall yield was still not satisfactory upon scale-up.[12] The central problem of the synthesis essentially arose from the tortuous nature of creating the C-3 and C-6 stereogenic centers in the caprolactam ring. The C-3 (*R*) configuration was established through double DKR operations. The substrate **9** with undesired C-3 (*S*) configuration, created through DKR resolution first in order to build up the desired C-6 (*S*) stereochemistry, must be corrected to the desired (*R*) configuration upon diastereoselective hydrogenation via laborious operation.

As depicted in Scheme 3, we envisioned that a more efficient synthesis could arise from direct construction of the desired C-6 (*S*) stereochemistry enantioselectively. An asymmetric addition of $MeNO_2$ to an α,β-unsaturated iminium intermediate formed by activating cinnamaldehyde **14** with an organocatalyst would provide the precursor **12** in one operation.[13] The field of organocatalysis has blossomed dramatically over the past decade. Its impact on synthetic chemistry is revolutionary, with numerous novel reactions being discovered. However, to date, their industrial applications have been mainly focused on medicinal chemistry on the small laboratory scale.[14a,15] An important advance in this field could be achieved if we could overcome the development challenges to implement/demonstrate the utility of organocatalysis on an industrial scale. The next synthetic challenge was to transform the desired substrate **11** to the seven-membered lactam. Therefore, condensation of aldehyde **12** with a glycine enolate equivalent **13** was required. This transformation is typically achieved via a Horner−Wadsworth−Emmons reaction. However, the phosphorus waste produced on industrial scale and lack of atom-economy were of concern to develop an environmentally responsible synthesis. To overcome this issue, it became clear that the application of a Knoevenagel-type condensation would be ideal, although the literature precedents for this type of transformation with glycine enolate equivalent **13** have been lacking.[16] Nevertheless, global reduction of nitro enamine **11** followed by alkylation and cyclization would deliver the caprolactam **2** and/or its C-3 epimer. Epimerization[9] of the C-3 amino stereogenic center would thus deliver the desired

(6) (a) Ho, T. W.; Ferrari, M. D.; Dodick, D. W.; Galet, V.; Kost, J.; Fan, X.; Leibensperger, H.; Froman, S.; Asaid, C.; Lines, C.; Koppen, H.; Winner, P. K. *Lancet* **2008**, *372*, 2115. (b) Ho, T. W.; Mannix, L.; Fan, X.; Assaid, C.; Furtek, C.; Jones, C.; Lines, C.; Rapoport, A. *Neurology* **2008**, *70*, 1305.

(7) (a) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311. (b) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307.

(8) For early syntheses, see ref 5 and (a) Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, S. L.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10*, 3235. (b) Steinhuebel, D. P.; Krska, S. W.; Alorati, A.; Baxter, J. M.; Belyk, K.; Bishop, B.; Palucki, M.; Sun, Y.; Davies, I. W. *Org. Lett.* **2010**, *12*, 4201. (c) Baxter, J. M.; Steinhuebel, D. P.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215. (d) Janey, J. M.; Orella, C. J.; Njolito, E.; Baxter, J. M.; Rosen, J. D.; Palucki, M.; Sidler, R. R.; Li, W.; Kowal, J. J.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 3212.

(9) Palucki, M.; Davies, I.; Steinhuebel, D.; Rosen, J. PCT Int. Appl. WO2007120589, 2007.

(10) Intermediate **4** could be prepared from 1,2-difluorobenzene in multiple steps; cf. ref 9.

(11) For a review, see: Brands, K. M.; Davies, A. J. *Chem. Rev.* **2006**, *106*, 2711.

(12) Approximately 12% overall yield to caprolactam **2** was obtained in hundred kilogram scale runs.

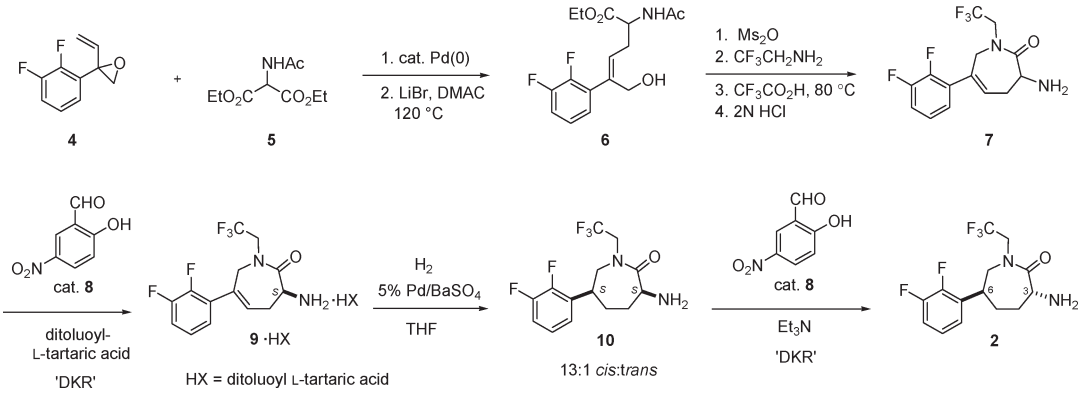
(13) (a) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (b) Palomo, C.; landa, A.; Mielgo, A.; Oiarbide, M.; Pugel, A.; Vera, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431. (c) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660. (d) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740. (e) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.* **2008**, 1232.

(14) For recent reviews, see: (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (b) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477. (c) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (d) Ley, S. V. *Asymmetric Synth.* **2007**, 201. (e) Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Chimia* **2007**, *61*, 224. (f) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (g) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

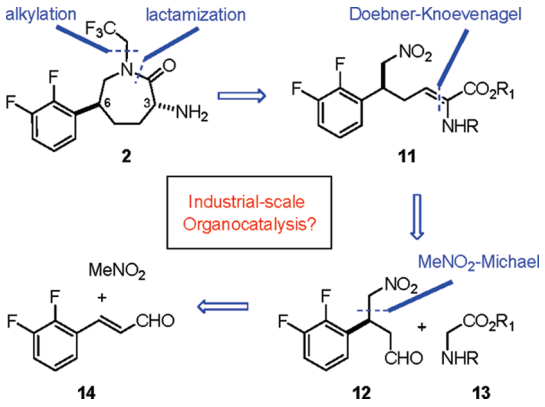
(15) For example, see: Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.

(16) For recent examples, see: (a) Bogen, S.; Arasappan, A.; Pan, W.; Ruan, S.; Padilla, A.; Saksena, A. K.; Girijavallabhan, V.; Njoroge, F. G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4219. (b) Velázquez, F.; Venkatraman, S.; Wu, W.; Blackman, M.; Prongay, A.; Girijavallabhan, V.; Shih, N.-Y.; Njoroge, F. G. *Org. Lett.* **2007**, *9*, 3061.

SCHEME 2. First Generation of Large Scale Synthesis of Caprolactam 2



SCHEME 3. Retrosynthetic Analysis of Caprolactam 2



caprolactam **2**, although a preferred, direct epimerization of caprolactam substrates without involving an imine intermediate[9] was unprecedented at the time of this work. Finally, to meet the high purity specifications (no new impurities >0.1%) required for acceptable use as an administered drug, it was crucial for our new long-term synthesis to be developed in such a way that the formation of impurities could be suppressed in each step without sacrificing yield and productivity. This article describes the successful realization of all of these goals, resulting in a highly efficient, environmentally responsible, asymmetric synthesis of telcagepant (**1**) via caprolactam **2**.

Results and discussion

Enantioselective 1,4-Addition of Nitromethane. Over the past decade, the advent of organocatalysis has brought revolutionary impact on synthetic chemistry at an extraordinary level. Rather than discovered, asymmetric iminium catalysis was the first organocatalytic activation mode designed for organic synthesis.[14a] By applying small organic molecules tailored to mimic biological processes, various novel chemical transformations have been achieved more effectively.[14] However, to the best of our knowledge, application of iminium organocatalysis on large scale has not been realized.[14] With the fast-growing interest in this relatively new field, asymmetric 1,4-addition of nitromethane to α,β-unsaturated aldehydes via a chiral iminium-ion species in the presence of chiral amine catalysts appeared in 2007.[13]

Our first attempt at an asymmetric addition of $MeNO_2$ to **14** under Hayashi's conditions[13a] (Table 1, entry 1) gave a promising result (50−75% yield) and more importantly confirmed that high enantioselectivity (95% ee) could be achieved by using the Jørgensen−Hayashi catalyst **15**.[17] However, after further scrutinizing the reaction profile and conditions, we quickly realized that the use of alcohol solvents led to the formation of undesired byproducts in the presence of the acidic cocatalyst $PhCO_2H$.[18] In particular, both **14** and product **12** could be trapped by alcohol solvents to form the corresponding acetal byproducts **16** and **17**, respectively. Although the reaction rate to form acetals was slower in *i*-PrOH than in MeOH, the acetal formation was inevitable and varied from batch to batch during development work. A quick solvent survey, however, confirmed that in Hayashi's system the use of alcohol solvents was crucial and optimal to obtain relatively higher yields and reasonable reaction rates. Unless we could overcome this limitation by developing a new system to include nonalcoholic solvents and to harness reaction pathways without sacrificing the yield, ee, and the reaction rate, this approach would not be suitable for further development.

Our preliminary results in dry aprotic solvents revealed that the reaction proceeded in very low conversion (<30%) or gave a complicated reaction profile (Table 1, entry 3; see also Supporting Information). However, the use of aqueous aprotic solvents did improve the conversion. Among the various solvents screened, aqueous THF was identified as the most promising solvent system. To further understand the reaction pathways and to restore the reactivity as well as the yield in nonalcohol solvents, the structures of several byproducts[19] were unambiguously elucidated (Figure 1). For mechanistic discussion about their formation, see Supporting Information.

After several experiments, a unique, effective "cocktail" catalyst system (*t*-$BuCO_2H$/$B(OH)_3$/5 mol % **15**) was discovered. The use of *t*-$BuCO_2H$ was essential to achieve a higher reaction rate and conversion; however, overcharging *t*-$BuCO_2H$ also had an adverse effect on the stability of product **12**, giving rise to a higher level of impurities including **20** (Table 1, entry 5).[20] In contrast, the use of $B(OH)_3$ as a

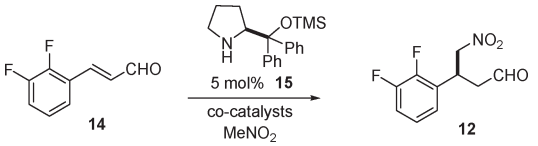
(17) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(18) $PhCO_2H$ was the optimal acid of choice in Hayashi's system; cf. ref 13a.

(19) Many low level impurities were formed during the reaction.

(20) Preliminary results revealed the use of a combination of $B(OH)_3$/*t*-$BuCO_2H$/**15** in aq THF effectively promoted enantioselective addition of $MeNO_2$ on cinammaldehydes.

TABLE 1. Selected Results of Asymmetric 1,4-Addition of $MeNO_2$[a]



entry	cocatalysts	$MeNO_2$ (equiv)	solvents	conditions	conversion (%)	yield (%)	ee (%)[b]	byproducts (%)
1	20 mol % $PhCO_2H$	6	MeOH	10 °C, 17 h	99	~50−75	95	**16a** (varied from 2 to 20%), **18** (< 0.5%), **19** (1%), **20** (2%)
2	10 mol % $PhCO_2H$	6	*i*-PrOH	20 °C, 25 h	98	~55−70	94	**16b** (varied from 1 to 15%), **18** (< 1%), **19** (1%), **20** (7.9%)
3	10 mol % $PhCO_2H$	6	MeCN	20 °C, 14 h	99	~20		**18** (< 1%), **19** (3.9%), **20** (72%)
4		3	10% H_2O−THF	20 °C, 63 h	96	58	95	**18** (< 1%), **20** (2.9%)
5	15 mol % *t*-$BuCO_2H$	6	25% H_2O−THF	20 °C, 14 h	94	65	96	**18** (< 1%), **19** (1.0%), **20** (7.2%)
6	100 mol % $B(OH)_3$	5	25% H_2O−THF	20 °C, 67 h	85	61	95	**18** (< 1%), **19** (1%), **20** (0.7%)
7	5 mol % *t*-$BuCO_2H$, 50 mol % $B(OH)_3$	6	17% H_2O−THF	20 °C, 29 h	94	73	95	**18** (< 0.1%), **19** (1.0%), **20** (2.8%)

[a]All reactions were carried out in the presence of 5 mol % of **15**. [b]The enantiomeric excess (ee) was determined by high performance liquid chromatography (HPLC) analysis: ChiralPak AD-RH column, 4.6 mm × 150 mm, 5 μm particle size, 45 °C, isocratic 0.1% aq H_3PO_4/MeCN/MeOH (30:45:25); flow rate 0.5 mL/min. HPLC sample preparation: **12** was converted to the corresponding hydrazone by treatment with 2,4-dinitrophenylhydrazine in aq H_3PO_4−MeCN at 40 °C for 5 min.

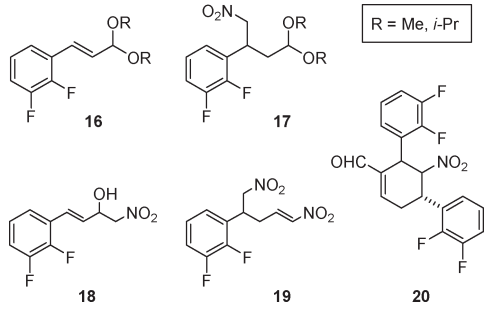
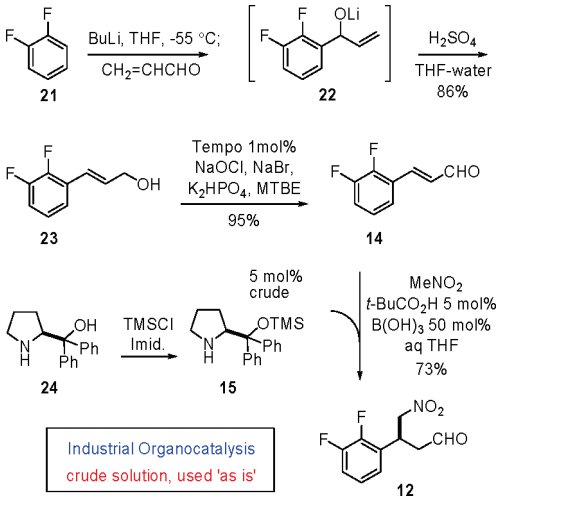


FIGURE 1. Identified byproducts formed during the asymmetric addition of $MeNO_2$ to **14**.

cocatalyst led to fewer impurities, albeit at the expense of a much slower reaction rate (Table 1, entry 6). *Interestingly, the use*[21] *of a combination of the weak acids t-BuCO$_2$H (5 mol %)/B(OH)$_3$ (50 mol %) allowed for the balance of the reaction efficiency and product stability*. As a result, the *t*-$BuCO_2H$ charge was reduced from 15 to 5 mol % without sacrificing the reaction rate or conversion (Table 1, entry 7), while the formation of impurities, especially **20**, was successfully suppressed to improve the yield significantly. It was believed that both the formation of the iminium-ion intermediate (from the condensation of **14** and **15**) and hydrolysis of the subsequent enamine intermediate (from the addition of $MeNO_2$ to the iminium-ion intermediate) to liberate the catalyst **15** were accelerated with the help of the acidic cocatalysts.[14] (For plausible reaction pathways, see Supporting Information.)

With the "cocktail" conditions for the preparation of **12** in hand, we then turned our attention to developing a cost-effective process to prepare **14**. Starting from inexpensive,

SCHEME 4. Process To Prepare Aldehyde 12 without Isolation of Any Intermediates[22]



commercially available 1,2-difluorobenzene (**21**),[22] **14** was efficiently prepared in a two-pot without isolating any intermediates (Scheme 4). 2,3-Difluorophenyllithium, generated in situ at ≤55 °C with *n*-butyl or *n*-hexyllithium to suppress its decomposition via 1,2-elimination,[23] was captured by acrolein to afford the 1,2-addition product **22**. The resulting alcohol **22** was then treated with sulfuric acid as a part of an aqueous workup so that the corresponding rearranged cinnamyl alcohol **23** was obtained in 86% assay yield.[24] TEMPO (1 mol %) catalyzed oxidation in MTBE/aq phosphate buffer at pH 10−11 gave the desired cinnamaldehyde **14** in 95% assay yield,[25]

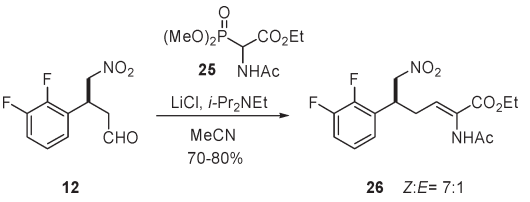
(21) The use of weak acids such as *t*-$BuCO_2H$ and $B(OH)_3$ does not interfere with the proper function of amine catalyst **15**. For an example of the acidity of *t*-$BuCO_2H$ and its interaction with amine bases, see: Xu, F.; Armstrong, J. D., III; Zhou, G. X.; Simmons, B.; Hughes, D.; Ge, Z.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **2004**, *126*, 13002.

(22) Unless otherwise mentioned, the processes described here were successfully carried out in a pilot plant on > 100 kg scale.

(23) Coe, P. L.; Waring, A. J.; Yarwood, T. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2729.

(24) The acid-promoted rearrangement had to be carried out at 60 °C. The conditions reported in the literature for a similar rearrangement did not work well for this substrate. Leleti, R. R.; Hu, B.; Prashad, M.; Repič, L. *Tetrahedron Lett.* **2007**, *48*, 8505.

SCHEME 5. Preparation of 25 via Horner−Wadsworth−Emmons Condensation



which was then directly subjected to the subsequent asymmetric $MeNO_2$-Michael addition.

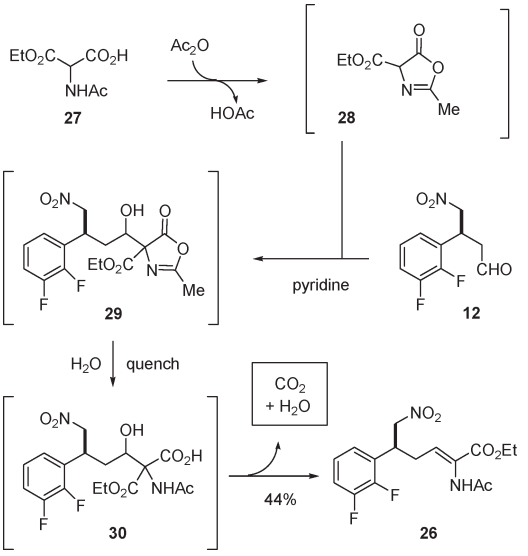
Further exhaustive screening of various chiral amines confirmed that the use of catalyst **15** was deemed optimal for the preparation of **12**. It is worthwhile to point out that the prolinol **24** had a much lower reactivity than that of the corresponding TMS-protected catalyst **15**. As the reaction pathways were harnessed under our cocatalyst system, the iminium organocatalysis on large scale performed extremely robustly. The crude catalyst **15**, prepared in the presence of TMSCl (1.3 equiv) and imidazole (1.7 equiv) in THF at 50 °C, was directly used after aqueous workup (Scheme 4). The final optimal conditions involved the use of nitromethane[26] (6 equiv) in 17% H_2O/THF in the presence of **15** (5 mol %), *t*-$BuCO_2H$ (5 mol %), and $B(OH)_3$ (50 mol %). Typically, after 30 h at ambient temperature, **12** could be reproducibly prepared in 73% assay yield and 95% ee. To minimize the degradation of the relatively unstable nitro aldehyde **12**, in practice, the crude solution of **12** was directly used for the next step without further purification.

Amine-Catalyzed Doebner−Knoevenagel Condensation. With the nitro aldehyde **12** secured, we turned our attention to a formal aldol condensation between **12** and a glycine anion equivalent **13**. A viable solution to this synthetic challenge would need to address the sensitive aldehyde and nitro functionalities of **12**, which are labile under basic conditions or at elevated temperature.

Application of a Horner−Wadsworth−Emmons condensation to install a glycine moiety was first explored. Appropriately mild conditions[27] were quickly found to accommodate the use of a glycine anion equivalent **25**[28] with aldehyde **12**. A slow addition of *i*-Pr_2NEt to a solution of **12** and **25** in the presence of LiCl in MeCN at 10−20 °C afforded the desired product **26** as a mixture of olefin isomers in 70−80% yield (Scheme 5).

The coupling reaction was effective; however, this approach was not atom-economical. In addition, the environmental burden for the disposal of phosphate byproducts and LiCl (3 equiv) was of concern for a route for the potential lifetime of the drug supply. This observation inspired us to develop an more environmentally responsible process by using readily available acetamidomalonate acid **27** as the source of a glycine anion

SCHEME 6. Condensation of Aldehyde 12 with 27 in Ac_2O−Pyridine and Its Plausible Pathways



equivalent, via a formal Doebner−Knoevenagel reaction,[29] to prepare enamine **26** (Scheme 6).[14] While efficient with aromatic aldehydes, this transformation usually gives low yields with enolizable aldehydes.[29]

Not surprisingly, treatment of **12** with Ac_2O/pyridine under similar conditions[29] afforded the desired product **26** in only 44% assay yield. The formation of azlactone **28**, generated *in situ* through the Ac_2O-mediated cyclodehydration of **27**, was crucial for the initial condensation with **12**. After further examination of the reaction mechanism, we noticed that intermediate **30**, key for decarboxylation, became available via azlactone ring opening of **29** only upon aqueous quench. At this point, it became clear that this transformation could be ultimately efficient if a desirable decarboxylation−elimination of **33** (Scheme 7), similar to **30**, could be achieved directly. We envisioned that **33** could arise from direct nucleophilic addition of glycine anion equivalent **27** or **32a** to iminium ion **31**, which could be easily accessed by condensation of an aldehyde with an amine.[30] Ideally, under these circumstances, only a catalytic amount of amine would be required since turnover of the amine is achieved through elimination of β-amino acid **33**. Indeed, the decarboxylation of **33** is reminiscent of a Doebner−Knoevenagel condensation of an aldehyde with $EtO_2CCH_2CO_2H$.[29] However, the use of

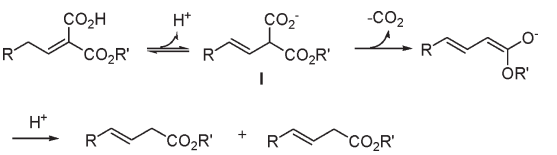
(25) Aldehyde **14** is a volatile solid and hence was not suitable for isolation via drying by suction or vacuum oven; however, its loss through concentration of solvents under reduced pressure was negligible. Although the same oxidation could be carried out in the presence of 0.1 mol% of AZADO, industrial utilization of AZADO is not feasible because of its availability and cost. Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

(26) For more discussion about optimization, see Supporting Information.

(27) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. P.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1984**, *50*, 2624.

(28) For a cost-effective preparation of **25**, see: Xu, F.; Devine, P. *Org. Process Res. Dev.* **2010**, *14*, 666.

(29) For lead references, see: (a) List, B.; Doehring, A.; Fonseca, M. T. H.; Jobb, A.; Torresa, R. R. *Tetrahedron* **2006**, *62*, 476. (b) Narsaiah, A. V.; Basak, A. K.; Visali, B.; Nagaiah, K. *Synth. Commun.* **2004**, *34*, 2893. (c) Ragoussis, N.; Ragoussis, V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3529 and references cited therein. For mechanistic discussion, see: (d) Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897. (e) Corey, E. J. *J. Am. Chem. Soc.* **1953**, *75*, 1163. The decarboxylation was believed to proceed via intermediate **I**.



(30) For example, see: Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669.

SCHEME 7. Proposed Pathways for Amine-Catalyzed Doebner–Knoevenagel Condensation via Iminium Intermediate 31

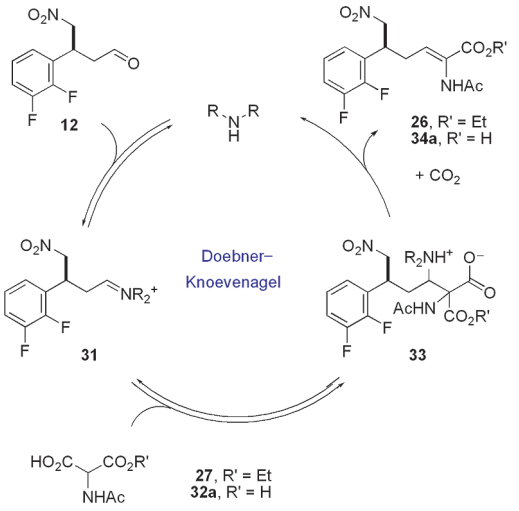


TABLE 2. Selected Results of Doebner–Knoevenagel Condensation of 12 and Mono-acid 27 at 20 °C

entry	amines	mol %	solvents	yield of **26**[a] (%)	*Z*:*E*[a]
1	DMAP	10	DMF	40	3:1
2	Et_3N	100	THF	0	
3	pyrrolidine	10	THF	85	2:1
4	pyrrolidine	100	THF	50	2:1

[a]The yield and *Z*:*E* ratio were determined by high performance liquid chromatography (HPLC) analysis: Agilent Eclipse Plus C18 column, 4.6 mm × 50 mm, 1.6 μm particle size, 25 °C, mobile phase 0.1% aq H_3PO_4/MeCN; flow rate 1.5 mL/min.

acetamidomalonic acid for a Doebner–Knoevenagel reaction promoted via an iminium species as proposed in Scheme 7 was unprecedented at the time of this work. In addition, extension of the use of amine catalysis concept to the Doebner–Knoevenagel variant with aliphatic aldehydes for selective preparation of α,β-unsaturated esters/acids is rare and leads predominantly to the formation of the corresponding the β,γ-unsaturated isomers under these conditions.[29] *The formation of the β,γ-unsaturated isomers suggested that the decarboxylation pathway under these classical conditions did not occur via an intermediate similar to **33**, which is fully consistent with Corey's mechanistic studies.*[29d] Furthermore, in the case of telcagepant, formation of the β,γ-unsaturated product would have destroyed the carefully established nitromethane-bearing benzylic stereogenic center.

Nevertheless, exploration of the primary/secondary amine-catalyzed Doebner–Knoevenagel condensation via an iminium intermediate (Scheme 7) was initiated. A breakthrough was achieved when it was discovered that pyrrolidine effectively facilitated the desired reaction. The use of 10 mol % of pyrrolidine afforded **26** in ~85% yield as a mixture of olefin isomers (*Z*:*E* = 2:1, Table 2, entry 3). In contrast, catalysis by DMAP afforded the desired product **26**, presumably via a less potent iminium-like species,[29a,b] in poor yield (~40%) along with the formation of many impurities (Table 1, entry 1).

Consistent with our mechanistic consideration (Scheme 7), the use of a weak tertiary amine base such as Et_3N, which could not form a corresponding iminium ion, resulted in no desired product (Table 2, entry 2). Furthermore, the reaction was cleaner and more efficient when a catalytic amount of pyrrolidine was used instead of a stoichiometric charge, as the decomposition of **12** was minimized (Table 2, entries 3 and 4).[31] In addition, introducing additional H_2O suppressed the desired reactivity, which is understandable as the formation of iminium species **31** became disfavored in the presence of extra water, although 1 equiv of water was formed during the reaction. Spontaneous decarboxylation, evidenced with CO_2 evolution observed as the reaction proceeded, confirmed the catalytic turnover of the amine.

TABLE 3. Selected Results of Doebner–Knoevenagel Condensation of 12 with Di-acid 32a in $AcNMe_2$ at 20 °C

entry	amine catalyst (15–20 mol %)	assay yield[a] of **34** (%)	*Z*:*E*
1	$(Bn)_2NH$	64	> 98:2
2	(Bn)MeNH	60	97:3
3	(*n*-Bu)MeNH	60	97:3
4	piperidine	60	97:3
5	pyrrolidine	85	91:9
6	**15**	0	

[a]The yield was determined by high performance liquid chromatography (HPLC) analysis: Ascentis Express C18 column, 4.6 mm × 100 mm, 2.7 μm particle size, 40 °C, mobile phase 0.1% aq H_3PO_4/MeCN; flow rate 2.0 mL/min.

The reaction was further extended to another unprecedented scope by using acid **32a**. We were pleased to find that free acid **32a** was a competent reagent for the desired condensation reaction in the presence of 15 mol % of pyrrolidine at ambient temperature, if the reaction was carried out in solvents such as DMF or $AcNMe_2$ that improved the limited solubility of **32a** (Table 3, entry 5). Ultimately, pyrrolidine was confirmed to be the most effective catalyst after the screening of various amines (Table 3). The steric bulk of the amine catalysts could dominate the efficiency of the reaction, as evidenced by the inactivity of the TMS-protected diphenylprolinol **15**, which was used in the preceding nitromethane addition step (Table 3, entry 6).

The successful extension of the reaction scope to the use of diacid **32a** offered a significant advantage. As such, pure acid **34a** could be isolated as its crystalline *n*-Bu_3N salt prior to its subsequent hydrogenation as outlined in the retrosynthetic plan (Scheme 3). This was deemed important because, in general, the performance of a hydrogenation reaction in terms of reaction rate and impurity profile is typically affected by the purity of the substrate. In addition, it was also a proper choice to conduct purification/isolation at this stage[32] especially since five steps had been carried out without any isolation/purification starting from difluorobenzene (**21**).

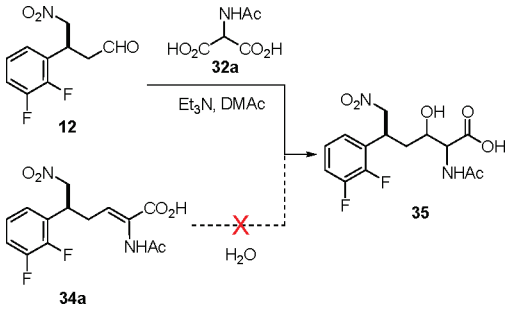
Although by using acid **32a** we had achieved the proof of concept of the strategy to prepare **34a** directly, **32a** was not suitable for large scale preparation due to safety concerns of its decomposition. In contrast, the corresponding disodium salt dihydrate **32b**[33] was quite stable. Unfortunately, the use of dihydrate salt **32b** did not result in the formation of any desired product **34a** under similar conditions. At this stage, it became clear that we had to develop a process involving

(31) Decomposition pathways including the self-condensation of aldehyde **12** catalyzed by amines were amplified with increasing pyrrolidine charge.

(32) The isomeric purity (olefin geometric isomers) was not required for the subsequent hydrogenation. However, isolation of the crystalline *n*-Bu_3N salt resulted in rejection of the *E* isomer (vide infra). Therefore, it was also vital to improve the *Z*:*E* ratio in order to maximize the isolated yield.

(33) For a practical, one-step preparation of disodium salt **32b**, see Supporting Information.

SCHEME 8. Preparation of Hydroxyl Impurity 35



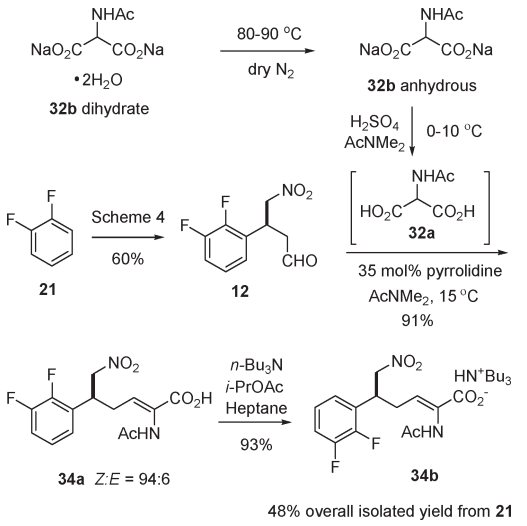
sequential salt break followed by Doebner−Knoevenagel condensation. To accept this target-orientated synthetic challenge, we thus needed to evolve the Doebner−Knoevenagel condensation to the next practical level by using sodium salt **32b** directly.

After several experiments, the use of H_2SO_4 became our acid of choice to liberate the free acid **32a** from **32b**, as the use of $AcNMe_2$ was an optimal solvent. We also noted that the salt break was most conveniently carried out by adding H_2SO_4 and **32b** in alternating portions in order to minimize the viscosity of the thick slurry on scale. From a stoichiometric standpoint, the condensation reaction was observed empirically to be more efficient when a slight excess of H_2SO_4 was used. In order to accommodate this increase in acid charge, the optimal pyrrolidine charge was increased to 35 mol %. With this understanding in hand, the Doebner−Knoevenagel condensation afforded **34a** in 82% assay yield. After aqueous workup,[34] **34a** was then isolated as its *n*-Bu_3N salt in 75% yield as the pure *Z* isomer.

However, further scrutiny of the isolated product **34a** led to the discovery of a new impurity **35** (~0.5−1%) in the isolated *n*-Bu_3N salt, leading to the formation of corresponding caprolactam impurities that could not be ultimately rejected in downstream chemistry. As such, we would have not been able to meet the high purity specifications required for pharmaceutical use.

The structure of **35** was unambiguously elucidated by applying NMR and LC/MS techniques. Indeed, treatment of **12** with **32a** in the presence of Et_3N did afford **35** in low yield along with numerous byproducts. By contrast, attempts to prepare **35** from the addition of H_2O to the acid **34a** were unsuccessful. After several carefully designed experiments, we concluded that an "uncatalyzed" low-yielding, direct coupling of **12** and **32a**, bypassing the pathway via iminium intermediate **31** (Scheme 8), was responsible for the formation of **35**. The 2 equiv of water brought into the system by the dihydrate salt **32b** could decrease the efficiency or rate of formation of the iminium species **31**, thereby rendering this background coupling competitive and, in fact, resulting in the formation of ~3% of **35**. In line with this observation, the use of the dried salt **32b**[35] led to a faster reaction rate and a higher yield (91% of *E* and *Z* isomers) with improved selectivity (*Z*:*E* = 94:6). More importantly, the formation of **35** was finally suppressed to < 0.4% in the crude reaction stream. The isolated *n*-Bu_3N salt **34a** contained only 0.1% of **35**, which met the high purity standards for preparing pure telcagepant.

SCHEME 9. Five-Step Process To Prepare 34b without Isolation of Any Intermediates



Thus, after several evolutions, a final manufacturing process for the Doebner−Knoevenagel condensation was developed.[36] In practice, to maintain the robustness of the process, 1.5 equiv of anhydrous salt **32b** was treated with 1.55 equiv of H_2SO_4 at 0−10 °C to create a slurry with acceptable viscosity. Further robustness was met by running the reaction at 15 °C in the presence of 35 mol % pyrrolidine to increase the stability of the acid **32a** formed *in situ*. Finally, *n*-Bu_3N salt **34b** was isolated in 80% yield with > 99% purity as its pure *Z* isomer and > 99% ee upgrade. Therefore, starting from 1,2-difluorobenzene (**21**), **34b** was thus obtained in 48% overall yield without isolation of any intermediates (Scheme 9).

Hydrogenation−Trifluoroethylation. With the preparation of enamine precursor **34b** established, we set forth for reduction of the nitro group to an amine so that the trifluoroethyl group could be installed. The use of commercially available trifluoroethyl triflate became our trifluoroethylation of choice. Attempts to convert the hydrogenated acid **36c** to **37** selectively were not successful as a result of *O*- versus *N*-alkylation competition. Although the *O*,*N*-bis-alkylated product **38** could be converted to desired **37**, the use of an excess of trifluoroethyl triflate to complete the reaction was not favored.

To overcome the *O*-alkylation issue, hydrogenated esters **36a,b** were subjected to trifluoroethylation (Scheme 10). Interestingly, because of the electronic effect of the *N*-trifluoroethyl group, the alkylated product **39** did not undergo further alkylation to **41**. However, the reduced methyl and ethyl esters **36a,b** were not particularly stable[37] with lactam **40** formed in up to 12% yield under these conditions. Fortunately, further studies showed that the formation of **40** could be eliminated by using the more sterically hindered isopropyl ester **42**.

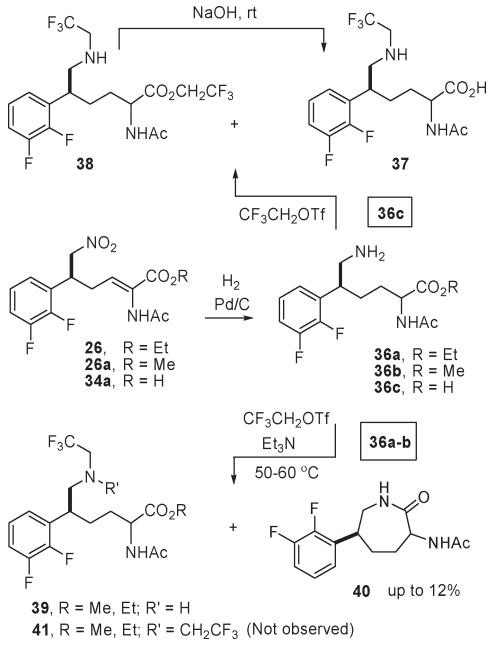
(34) The extraction of **34a** into aqueous phase was inefficient below pH 8, and **34a** decomposed slowly above pH 9. To extract **34a** into *i*-PrOAc, the aqueous phase was acidified to pH 2−3. Above pH 3 the extraction was inefficient, and **34a** slowly decomposed below pH 2.

(35) Dehydrated at 80−90 °C in vacuum with dry N_2 sweep.

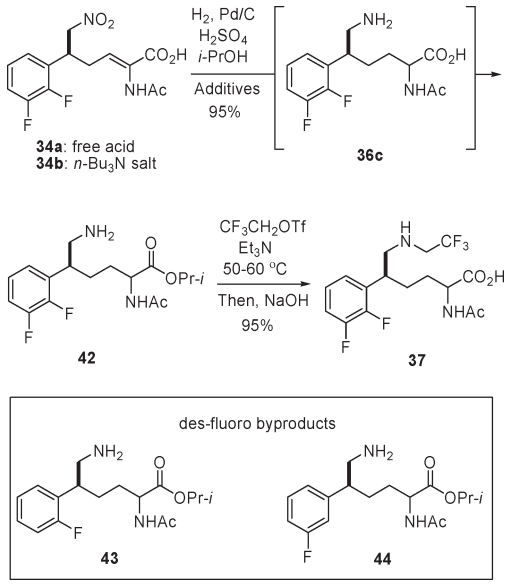
(36) Further studies on the reaction scope of this novel Doebner−Knoevenagel coupling and its application will be reported in due course.

(37) Esters **36a,b** could slowly convert **40** upon storage at ambient temperature after several weeks.

SCHEME 10. Reduction and Trifluoroethylation



SCHEME 11. One-Pot Synthesis of Acid 37



A streamlined synthesis required the formation of isopropyl ester **42** *in situ* during hydrogenation. Thus, to promote a one-pot hydrogenation/esterification, **34b** was subjected to hydrogenation in *i*-PrOH in the presence of H_2SO_4 and Pd−C at 50 °C (Scheme 11). Unfortunately, significant levels of desfluoro diastereomers **43** (up to 2.5%) were observed, while the other desfluoro isomers **44** were present at $<0.05\%$.[38] In addition, rejection of the desfluoro impurities was poor in downstream chemistry. With this in mind, we realized that **43** had to be suppressed to $<0.2\%$ in the crude reaction. Otherwise, telcagepant produced from this route would not meet the required high purity specifications.

Indeed, the highly restrictive standards for impurity tolerance in the pharmaceutical industry make the hydrogenation more challenging for suppression of desfluoro impurities. Although dehalogenation is often observed under heterogeneous hydrogenation conditions, in general, effective protocols to suppress dehalogenation to date have been lacking. Among the reported methods,[39] the use of Lewis acids such as $ZnBr_2$ and $ZnCl_2$ to modulate the Pd, Pt catalysts and minimize dechlorination/debromination of aromatics is attractive.[40] However, this protocol has not been extended to suppress defluorination. Interestingly, after several control experiments, preliminary results showed that exposure of the free acid **34a**, obtained after salt break in aq HCl/EtOAc containing ~30 mol % of *n*-$Bu_3N^+HCl^-$,[41] to the hydrogenation conditions used for salt **34b** resulted in only ~0.2% of desfluoro byproduct **43** (Table 4, entry 4).[42] Although introducing a salt break of **34b** to **34a** was not ideal for a manufacturing route, this result, in line with the literature regarding dehalogenation, encouraged us to initiate an exhaustive screening with chloride additives to suppress defluorination during the hydrogenation of salt **34b**.

The screening results are summarized in Table 4. In terms of robustness and reaction rate, the Pearlman catalyst (Pd-$(OH)_2$-C) was superior to all other catalysts screened. The use of $ZnCl_2$ reduced defluorination to 0.6% but was not powerful enough to meet our requirement for $<0.2\%$ defluorination (Table 4, entry 6). *However, introducing soluble, noncovalently bonded chloride sources* (*Table 4, entries 2*−*5*) *dramatically suppressed the formation of desfluoro impurities*. In contrast, the use of insoluble NaCl showed minimal improvement to suppress the defluorination (Table 4, entry 7). After extensively screening various salts or acids, the use of LiCl became our additive of choice to effectively suppress defluorination.

At this point, although we had achieved proof of concept of the strategy to prepare **37** directly from **34b** and to suppress defluorination, a large amount of optimization remained in order for the one-pot process to be viable for a commercial manufacturing process. The chemistry was further optimized by carefully understanding the effect of each factor on defluorination as well as on hydrogenation. Furthermore, we found that conversion and defluorination were relatively insensitive to reaction temperature. The use of less LiCl, higher pressure, and relatively higher catalyst loading led to higher conversion, faster reaction rate, and relatively higher levels of defluorination. In contrast, introducing excess LiCl as well as other chloride sources led to a significant decrease in reaction rate, as the defluorination was minimized, presumably due to decreased catalyst activity. Furthermore, the use of higher catalyst loading beyond the optimal 10−15 wt % range led to a significant increase of

(38) The structures of the desfluoro impurities were unambiguously characterized by applying LC/MS techniques and by synthesizing authentic samples.

(39) For a lead reference, see: Mallat, T.; Baiker, A. *Appl. Catal., A* **2000**, *200*, 3.

(40) Wu, G.; Huang, M.; Richards, M.; Poirier, M.; Wen, X.; Draper, R. W. *Synthesis* **2003**, 1657.

(41) Because of its hydrophobicity, *n*-$Bu_3N^+HCl^-$ tends to remain in the organic phase.

(42) Studies also showed that **43** was not generated under hydrogen-starved conditions, which could result in defluorination. For example, see: Brands, K. M. J.; Krska, W.; Rosner, T.; Conrad, K. M.; Corley, E. G.; Kaba, M.; Larsen, R. D.; Reamer, R. A.; Sun, Y.; Tsay, F. *Org. Process Res. Dev*. **2006**, *10*, 109.

TABLE 4. Selected Results of Hydrogenation of 34b and Effects of Additives on Defluorination[a]

entry	catalysts (10 wt % loading)	additives	H_2 (psig)	temp (°C)	isomers of desfluoro **43**[b] (%)	conversion[b] (%)
1	10% $Pd(OH)_2$-C		50	50	1.06−2.5	>99
2	10% $Pd(OH)_2$-C	LiCl, 0.3 equiv	75−100	35	0.12	98
3	10% $Pd(OH)_2$-C	35% HCl, 0.3 equiv	100	35	0.17	97
4	10% $Pd(OH)_2$-C	n-$Bu_3NH^+Cl^-$, 0.3 equiv	100	35	0.12	94
5	10% $Pd(OH)_2$-C	$Et_3NH^+Cl^-$, 0.3 equiv	100	35	0.15	92
6	10% $Pd(OH)_2$-C	$ZnCl_2$, 0. Five equiv	100	50	0.61	95
7	10% $Pd(OH)_2$-C	NaCl, 0.5 equiv	100	50	0.78	99
8	5% Pd/C shell	LiCl, 0.5 equiv	100	50	<0.02	65
9	$Pd/BaSO_4$	LiCl, 1.0 equiv	100	50	<0.02	20

[a]For more screening results, see the Supporting Information. [b]Upon completion of esterification, the desfluoro impurities as well as the conversion were determined by high performance liquid chromatography (HPLC) analysis: Ascentis Express C18, 4.6 mm × 100 mm, 2.7 μm particle size, 40 °C, mobile phase 0.1% $HClO_4$/MeCN; flow rate 2.0 mL/min.

43 as the reaction was overexposed to hydrogenation. The effect of the chloride anion has been studied in depth for production of consistent hydrogenation results, but its mechanism remains unclear. In conclusion, an effective protocol to suppress defluorination by introducing soluble Cl^- to hydrogenation was achieved.

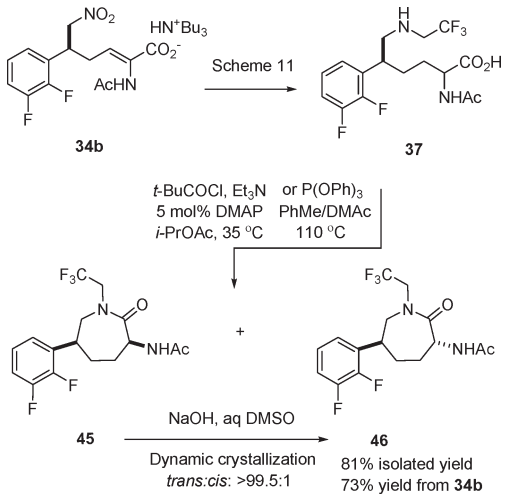
Taking into consideration the overall influence of each factor, optimally balanced conditions were obtained. Hydrogenation of salt **34b** was thus performed in the presence of 0.3 equiv of LiCl, 2.5 equiv of H_2SO_4, and 10−15 wt % of 10 wt % $Pd(OH)_2$-C (50% wet) at 50−100 psig of hydrogen between 35 and 50 °C. As a result, upon achieving completion of the esterification of the crude hydrogenated mixture of **36c** and **42** via azeotropic distillation at 65−70 °C, the defluorination impurity **43** was reproducibly suppressed to <0.2% in the crude reaction stream, thus securing a process to produce telcagepant which met the quality requirements of the pharmaceutical industry.

Et_3N was added to the above crude hydrogenation stream of **42** to neutralize the acids. Once the trifluoroethylation was brought to completion with 1.1 equiv of CF_3CH_2OTf (Scheme 10),[43] the reaction was quenched with aq NaOH while ester **42** was simultaneously hydrolyzed. The resulting crude acid **37** was extracted into *i*-PrOAc at pH 4−5 in >95% yield and most of n-Bu_3N was removed during the aqueous workup for the ease of the isolation of subsequent product.

Cyclization. Our initial cyclization process called for the use[44] of $P(OPh)_3$ as a dehydration promoter at ~110 °C in toluene−$AcNMe_2$, which effectively gave the desired diastereomers **45/46** in 87% assay yield. Despite of the efficiency of this cyclization,[45] the search for an environmentally friendly "green" process continued due to our concerns regarding the phosphorus waste and phenol generated during the cyclization.

Taking advantage of the decreased nucleophilicity[46] of the nitrogen tethered with the trifluoroethyl group, we envisioned that the formation of the caprolactam ring could be realized via an appropriate anhydride species, selective formation of which could be possible by activating the carboxylate without acylating the secondary amine moiety. Indeed, after several experiments, we were pleased to find that slowly introducing 1.2 equiv of *t*-BuCOCl at 35 °C in the presence of

SCHEME 12. Process To Prepare 46 without Isolation of Any Intermediates



5 mol % of DMAP and 2.1 equiv of Et_3N in *i*-PrOAc was extremely efficient in promoting the desired cyclization and affording a mixture of diastereomer **45**/**46** in 89% assay yield[47] (Scheme 12).

At this stage, a further streamlined synthesis of talcagepant would require the development of a base-catalyzed, dynamic crystallization process[30] to isolate the desired **46** by epimerizing the undesired isomer **45**. It should be noted that a selective epimerization of a C-3 amino capolactam without involving an *in situ* formation of an imine intermediate[9] was not well studied at the time of this work. After screening several conditions, we found that treatment of **45** with strong bases such as NaOH in aq DMSO promoted the epimerization cleanly and effectively. The desired caprolactam **46** was stable under these conditions, and neither hydrolysis of the acetamide nor caprolactam ring opening was observed. The thermodynamic equilibrium ratio of **46**:**45** in homogeneous aq NaOH−DMSO was determined to be 97:3 at ambient temperature. In practice, after aqueous workup, the crude reaction mixture of **45** was simply subjected to aq NaOH−DMSO for crystallization at 50 °C. The desired **46** was thus isolated in 81% yield and >99% purity, while >99% of the undesired **45** was converted to **46** under this preferential crystallization conditions.

(43) The resulting weak acid HSO_4^- from Et_3N neutralization did not affect the alkylation.

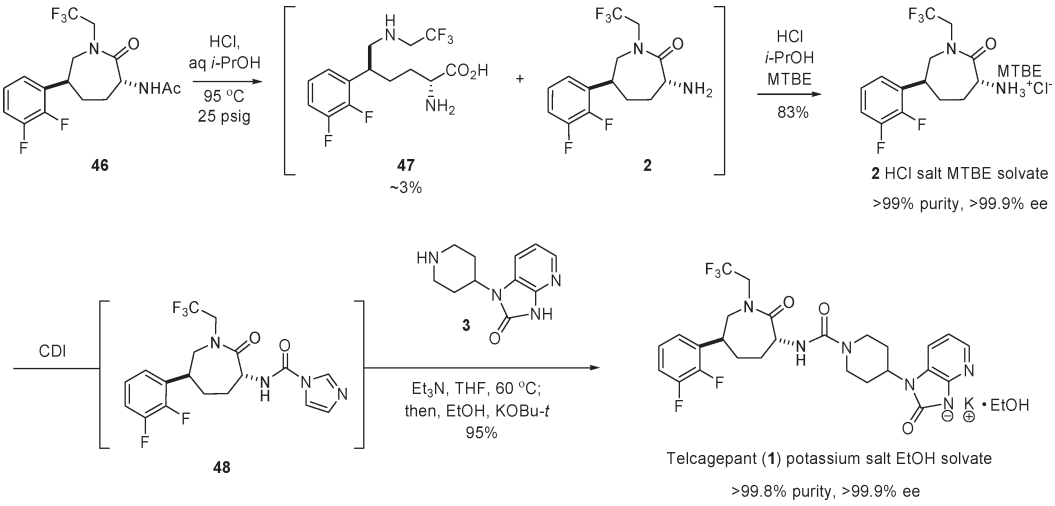
(44) For example, see : Mitin, Y. V.; Glinskays, O. V. *Tetrahedron Lett.* **1969**, *60*, 5267.

(45) It is interesting to note that intramolecular ring closure of **37** could also occur just by heating the acid **37** itself in solvents such as $AcNMe_2$, although the reaction was extremely slow (~10% conversion after 1 week).

(46) The decreased nucleophilicity was evidenced by unsuccessful bistrifluoroethylation of **39** under various conditions (vide supra).

(47) The effect of concentration on reaction yield is not significant. Typically, the reaction was carried out in ~0.25 M of **37**. Interestingly, starting from 1:1 mixture of **37**, the ratio of **46**:**45** was increased to ~3:1−4:1 during the cyclization by using either $P(OPh)_3$ or *t*-BuCOCl. Resubjecting a mixture of **45**/**46** to the cyclization conditions did not result in a ratio change.

SCHEME 13. Endgame of Telcagepant Synthesis



In summary, sequential hydrogenation, alkylation, and cyclization in combination with efficient epimerization/crystallization workup made this robust through-process extremely efficient. Starting from *n*-Bu_3N salt **34b**, **46** was obtained in 73% overall yield without isolation of any intermediates.

Endgame. As mentioned above, acetamide **46** is stable against hydrolysis under basic conditions. After evaluating various conditions, the use of HCl in aq *i*-PrOH became our hydrolysis of choice. Treatment of **46** with 6.7 equiv of concd HCl in a solution of *i*-PrOH/water (2:1) at 80 °C for ~17 h gave the desired amine **2** in 85% assay yield. The byproduct acid **47** was reduced from 7% to 0.5% through a simple aqueous workup.

Although the process had produced caprolactam **2** in a decent yield, even a small improvement in chemical yield at a late stage of the synthesis would result in a significant benefit to a manufacturing route. With more experiments carefully designed to understand each factor affecting the hydrolysis, we found that the formation of the acid **47** could be substantially reduced by further decreasing the HCl charge, although reducing the reaction rate significantly. To overcome the decrease in reaction rate caused by lowering the HCl charge, the hydrolysis was thus carried out at 95 °C under pressure (25 psig of N_2). This simple modification, easily implemented in large scale preparation, successfully reduced the formation of the acid **47** to ~3% and improved the yield to 90%. Finally, **2** was isolated as its HCl salt MTBE solvate in 83% yield in >99% purity with near perfect ee (Scheme 13).[48]

Finally, with caprolactam **2** MTBE solvate HCl salt in hand, the new synthesis merged with the previously reported synthesis of talcagepant in the last coupling step.[5,8,9] Treatment of **2** with CDI in the presence of Et_3N followed by addition of **3** afforded telcagepant **1**, which was then isolated as its potassium salt EtOH solvate in 92% yield with >99.8% purity and >99.9% ee. Thus, the new synthesis met all quality attributes in the pharmaceutical industry.

Conclusion

In summary, a highly efficient, asymmetric synthesis of telcagepant (**1**) suitable for implementation on the manufacturing scale has been described. The entire synthesis is carried out with a minimum number of isolations and operations. The synthesis features the first application of iminium organocatalysis on industrial scale. The key to the success of our application is to overcome the development challenge by developing a unique organocatalyst "cocktail" system (5 mol % *t*-$BuCO_2H$/50 mol % $B(OH)_3$/5 mol % **15**) to harness the reaction pathways. As such, the C-6 stereogenic center via an iminium species is practically established in one operation in >95% ee. Furthermore, a subsequent novel Doebner−Knoevenagel reaction catalyzed by pyrrolidine, which is also via an iminium species, has been thoroughly developed so that the preparation of **34b** is achieved efficiently by utilizing the crude **12** and diacid sodium salt **32b**. Guided by a mechanistic understanding of the Doebner−Knoevenagel reaction, a full control of the suppression of the hydroxyl impurities **35** has been realized. Starting from commercially available 1,2-difluorobenzene, a robust through-process affords the crystalline enamine acid *n*-Bu_3N salt **34b** in 48% isolated overall yield and >99% purity. One-step global hydrogenation/esterification affords the amine **42** in high yield. In order to produce pure telcagepant for clinical use, a practical and effective protocol was developed to suppress the formation of the desfluoro byproducts during the hydrogenation; as such, defluorination in the presence of LiCl could be reproducibly controlled to <0.2%. After trifluoroethylation of **42**, an efficient lactamization in the presence of *t*-BuCOCl followed by a base-catalyzed dynamic crystallization delivers caprolactam acetamide **46**, the second isolated crystalline solid in this synthesis, in >99% purity, >99% ee, and 73% yield over three steps. Finally, coupling caprolactam **2** with **3** completes the synthesis of telcagepant (**1**, >99.8% purity and >99.9% ee). Isolating only three intermediates, the overall yield of this cost-effective synthesis is up to 27%.

The route described in this manuscript is an example of a synthetic target driving the discovery of new chemistries: an industrial application of a dual acid cocatalyst system for enantioselective 1,4-addition of nitromethane, a novel amine-catalyzed Doebner−Knoevenagel type of coupling as well as a discovery in suppressing the formation of desfluoro impurities under hydrogenation conditions. Containing all of the elements required for a manufacturing process, the route is efficient and prepares **1** with the high quality required for pharmaceutical

(48) Alternatively, the hydrolysis could be performed in aq HCl/HOAc to afford a similar yield. However, robust rejection of process impurities was obtained through hydrolysis of **2** in aq HCl/*i*-PrOH.

use. More importantly, practicing the philosophy of "green chemistry", the synthesis of telcagepant was developed with a strong interest to minimize the waste and maximize the measures taken to protect our environment without sacrificing the efficiency of the synthesis. The success of our synthesis, as a result of target-oriented and mechanism-guided development, clearly demonstrates the importance of developing an environmentally responsible class of chemistry.

Experimental Section[49]

(*E*)-3-(2,3-Difluorophenyl)acrylaldehyde (14). To a solution of 1,2-difluorobenzene (**21**, 4.80 kg, 42.1 mol) in THF (38.4 L) in a 100 L flask was added *n*-hexyllithium (2.3 M in hexane, 19.21 L, 44.2 mol) dropwise over 3 h, while the internal temperature was maintained at ≤55 °C. The resulting slurry was aged at −60 to −55 °C for additional 0.5 h. A solution of acrolein (3.26 L, 46.3 mol) in THF (5 L) was then added dropwise over 2.5 h. After additional 30 min at −60 to −55 °C, the cold reaction solution was inverse quenched into water (25 L). The aqueous layer was discarded. To the organic layer was added an aq H_2SO_4 solution (6.0 L of 96% H_2SO_4 + 13.4 L of water). After the reaction mixture was agitated at 60 °C overnight under nitrogen and cooled to ambient temperature, the layers were separated. The aqueous layer was extracted with toluene (20 L). The combined organic phase was washed with water (24 L) followed by half-saturated sodium bicarbonate (12 L). The organic layer was then concentrated under reduced pressure to ∼10 L, and the crude was used directly in the next step. HPLC assay: 6.195 kg of the desired product **23**; 86% assay yield.

Sodium bromide (0.74 kg, 7.21 mol), potassium phosphate dibasic (3.14 kg, 18.02 mol), and water (11.67 L) were charged to a 100 L vessel. The solution pH was adjusted to 10.5−11.0 with 1 N KOH (∼2.5 L). A solution of the crude alcohol **23** (9.725 kg, 63.05 wt % solution in MTBE/toluene, 36.0 mol), MTBE (34.0 L), and TEMPO (0.056 kg, 0.360 mol) were added at ambient temperature. The reaction solution was cooled to ∼10 °C. Sodium hypochlorite (Chlorox, 39.7 L, 6.15 wt %, 36.0 mol) was added dropwise over 2 h, while the internal temperature was maintained at 10−15 °C. The aqueous layer was removed at ambient temperature, and the organic phase was washed with 0.1 M $Na_2S_2O_3$ (10 L) followed by half-saturated aqueous sodium bicarbonate (10 L). The organic phase was concentrated to ∼130 L, and solvent-switched to THF at constant volume under reduced pressure by feeding THF. The residual MTBE was less than 0.5%, and the residual toluene was less than 10%. The desired organic layer was used directly in the next step. HPLC assay: 95% assay yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (d, J = 7.6 Hz, 1 H), 7.55 (d, J = 16.4 Hz, 1 H), 7.27 (m, 1 H), 7.17 (m, 1 H), 7.08 (m, 1 H), 6.71 (dd, J = 16.4, 7.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 151.1 (dd, J = 250.0, 12.8 Hz), 149.4 (dd, J = 256.2, 13.7 Hz), 143.4 (t, J = 3.4 Hz), 131.7 (d, J = 5.6 Hz), 124.8 (dd, J = 7.2, 4.8 Hz), 124.5 (d, J = 8.4 Hz), 123.6 (d, J = 3.4 Hz), 119.7 (d, J = 17.1 Hz). Anal. Calcd for $C_9H_6F_2O$: C, 64.29; H, 3.60. Found: C, 63.89; H, 3.26.

(*E*)-3-(2,3-Difluorophenyl)prop-2-en-1-ol (23). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 1 H), 7.05 (m, 3 H), 6.77 (d, J = 16.1 Hz, 1 H), 6.49 (dt, J = 16.1, 5.4 Hz, 1 H), 4.37 (dd, J = 5.4, 1.2 Hz, 2 H), 1.65 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2 (dd, J = 247.7, 12.8 Hz), 148.5 (dt, J = 250.5, 13.5 Hz), 132.9 (d, J = 4.8 Hz), 127.0 (d, J = 9.6 Hz), 124.0 (dd, J = 7.2, 4.8 Hz), 122.5 (t, J = 3.4 Hz), 122.4 (t, J = 3.1 Hz), 116.1 (d, J = 17.2 Hz), 63.78. Anal. Calcd for $C_9H_8F_2O$: C, 63.53; H, 4.74. Found: C, 63.85; H, 4.53.

(49) Unless otherwise mentioned, the processes described here in much larger scale were carried out in pilot plant successfully and reproducibly.

(*S,Z*)-2-Acetamido-5-(2,3-difluorophenyl)-6-nitrohex-2-enoic Acid Tri-*n*-butylamine Salt (34b). A concentrated solution of aldehyde **14** prepared as above (1.189 mol assay, 200 g of **14**) was diluted with THF to a volume of 2.8 L. H_2O (400 mL), pivalic acid (6.08 g, 0.0594 mol), boric acid (36.78 g, 0.594 mol), TMS-prolinol **15** (19.36 g assay, 0.0594 mol, ∼250 mL solution in THF/MTBE; for its preparation, see Supporting Information) and nitromethane (436 g, 7.143 mol) were added at ambient temperature. The resulting homogeneous solution was stirred at ambient temperature for 30 h (>94% conversion[50]). The reaction solution was cooled to 2−7 °C and quenched by addition of *i*-PrOAc (2 L), 15% aq NaCl (600 mL), and 1 N HCl (200 mL). The organic layer was washed with 6% $NaHCO_3$ in 5% aq NaCl (1 L) and 15% aq NaCl (600 mL × 2). The organic phase was azeotropically dried and solvent-switched to *i*-PrOAc while maintaining the internal temperature at <15 °C. The final solution (∼2 L, ∼10 wt % of **12**) was directly used in the subsequent step or could be stored at 5 °C; 73−75% assay yield of **12**; ∼95% ee.

A three-neck flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet was charged with Me_2NAc (700 mL) and anhydrous di-Na salt **32b** (134.2 g, 0.654 mol). To the resulting slurry at 0−10 °C was added H_2SO_4 (96%, 75.0 mL, 1.352 mol) dropwise while the internal temperature was maintained at <10 °C with external cooling. The slurry was agitated at 0−10 °C for 1 h, and more anhydrous di-Na salt **32b** (134.2 g, 0.654 mol) was added in portions over 1−2 h. The resulting slurry was agitated between 0 and 10 °C for 4−6 h. Pyrrolidine (25.5 mL, 0.306 mol) was then added dropwise. The slurry was aged between 0 and 10 °C for 30 min. Then, nitro aldehyde **12** (0.8727 mol assay, 200 g of **12** in ∼2 L of *i*-PrOAc) was charged over 30 min. The reaction mixture was aged between 15 and 20 °C for 20−24 h. Aqueous Na_2CO_3 (4 wt %, ∼3.5 L) was added to adjust the pH to 8−9 while the internal temperature was maintained at <25 °C. The desired aq phase was separated at 20−25 °C. *i*-PrOAc (1.8 L) was added. The biphasic solution was adjusted to pH = 2−3 by adding 5 N HCl (∼700 mL) slowly. The organic phase was separated, and the aq phase was extracted with *i*-PrOAc (600 mL). The combined organic phase was washed with brine (15 wt %, 300 mL); 91% assay yield of *E* and *Z* isomers (261 g, *Z*:*E* = ∼95:5). The organic phase was azeotropically dried and solvent switched to *i*-PrOAc at a volume of ∼1.23 L.

A 5 L flask equipped with a reflux condenser and an overhead stirrer was charged with *n*-Bu_3N (267 mL, 1.121 mol) and *i*-PrOAc (735 mL). After about ∼15% (370 mL) of the above *i*-PrOAc solution of the free acid **34a** was charged dropwsie at 45 °C, the batch was seeded with *n*-Bu_3N salt **34b** (1.9 g) and agitated at 45 °C for 1−2 h. The remaining *i*-PrOAc solution of the free acid **34a** was added at 45 °C over 3−4 h. The resulting slurry was aged at 45 °C for an additional 1 h, and then heptane (980 mL) was added dropwise at 45 °C over 3 h. The resulting slurry was aged at 45 °C for 1 h. The batch was gradually cooled to 0−5 °C over 3 h and stirred at 0−5 °C for 3−6 h. The solids were collected by filtration and washed with 40% heptane/*i*-PrOAc (735 mL × 2) while maintaining the batch temperature at 0−5 °C. Drying at 45 °C in vacuum afforded the desired *n*-Bu_3N salt **34b** (359 g) in >99% *Z* diastereomer and 99.1% ee; 80% isolated yield from **12**. ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.02 (s, 1 H), 7.33 (m, 1 H), 7.29 (m, 1 H), 7.21 (m, 1 H), 6.14 (t, J = 6.8 Hz, 1 H), 4.95 (m, 2 H), 3.91 (m, 1 H), 2.42 (m, 6 H), 1.92 (s, 3 H), 1.38 (m, 6 H), 1.27 (m, 6 H), 0.87 (t, J = 7.3 H, 9 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 167.8, 166.1, 149.7

(50) Nitroaledehyde **12** gave a broad peak by HPLC assay, which was difficult to monitor and assay. However, treatment of **12** with 2,4-dinitrophenylhydrazine gave the corresponding hydrazone derivative quantitatively, which gave a sharp peak by both chiral and achiral HPLC assays. HPLC sample preparation: To a solution of 2,4-dinitrophenylhydrazine (∼10 mg/mL in MeCN, 2 mL) and H_3PO_4 (25 μL) in a 25 mL volumetric flask was added the reaction solution (∼100 μL). The resulting solution was aged at 40 °C for 5 min and diluted to 25 mL with acetonitrile prior to use.

(dd, J = 245.5, 13.0 Hz), 148.2 (dd, J = 246.9, 12.9 Hz), 130.8, 129.4 (d, J = 10.6 Hz), 127.9, 125.1 (dd, J = 6.7, 4.3 Hz), 124.1, 116.3 (d, J = 16.4 Hz), 78.3, 51.7, 35.8, 30.6, 26.0, 22.7, 19.7, 13.6. Anal. Calcd for $C_{26}H_{41}F_2N_3O_5$: C, 60.80; H, 8.05; N, 8.18. Found: C, 60.65; H, 8.09; N, 8.22.

***N*-((3*R*,6*S*)-6-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-azepan-3-yl)acetamide (46).** A mixture of *n*-Bu_3N salt **34b** (150 g, 0.292 mol), H_2SO_4 (96%, 40.5 mL, 0.73 mol), LiCl (3.71 g, 0.0876 mol), and Pearlman's catalyst (20 g, 10 wt % $Pd(OH)_2$ on carbon contained ~50% water) in *i*-PrOH (900 mL) was hydrogenated under 50 psig H_2 at 40 °C for ~20 h. The catalyst was removed through filtration and washed with *i*-PrOH (300 mL). The combined filtrate was azeotropically dried (KF < 1000) under vacuum with *i*-PrOH, while the internal temperature could be maintained at 60 °C. The reaction solution was aged at 60−65 °C for 8 h to complete esterification (> 98% conversion). Then, the batch was further concentratde to a volume of ~500 mL and KF < 3000; 95% assay yield of the hydrogenated amine ester **42** (95 g assay in ~500 mL *i*-PrOH, 0.278 mol). Et_3N (174 mL, 1.25 mol) was added at ambient temperature dropwise. The solution was then warmed to 55 °C, and CF_3CH_2OTf (50 mL, 0.347 mol) was added dropwise over 1−2 h while the reaction temperature was maintained between 50 and 60 °C. The reaction solution was aged at 60 °C for 8 h until > 99% conversion was achieved. The reaction solution was then cooled to ambient temperature, and 5 N NaOH solution (306 mL, 1.53 mol) was added dropwise over 0.5−1 h. The resulting solution was stirred for 1−2 h at 30−35 °C until the saponification of the ester was deemed complete by HPLC: > 99% conversion. The reaction was cooled to ambient temperature, and water (300 mL) and heptane (500 mL) were added. To the separated aq phase was added 6 M HCl (~150 mL) dropwise to adjust pH = 4−5, while the internal temperature was maintained at < 25 °C with external cooling. The aq phase was extracted with *i*-PrOAc (1.2 L). The organic phase was washed with 15 wt % brine (400 mL) and azeotropically dried with *i*-PrOAc in vacuum to a volume of 1.1 L (KF < 1000, < 2 vol % *i*-PrOH); 95% assay yield of **46** (101 g assay, 0.264 mol). DMAP (13.2 mmol, 1.61 g) and Et_3N (77.3 mL, 0.554 mol) were added. Then, trimethylacetyl chloride (39 mL, 0.317 mol) was added dropwise over 1 h at 35−40 °C. The reaction mixture was stirred for additional 5−8 h until > 99% conversion was achieved. The reaction mixture was cooled to ambient temperature and quenched with 1 N HCl (350 mL). The organic phase was washed with 7.5% $NaHCO_3$ (440 mL). The organic layer was solvent switched to DMSO (500 mL) in vacuo at 60 °C, and 2.5 N NaOH (260 mL) was added dropwise while the internal temperature was maintained at < 30 °C. After aging 30 min, the batch was seeded and agitated overnight at ambient temperature. Water (240 mL) was added dropwise over 1−2 h to adjust the DMSO−water ratio to 1:1. The slurry was aged for 2 h at ambient temperature before filtration. The wet cake was washed with DMSO−water (1:1, 160 mL) followed by water (320 mL). Vacuum drying in vacuum at 55 °C under nitrogen gave 78 g of the desired product **46**; 73% overall yield from **34b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (m, 2 H), 7.0 (d, J = 6.0 Hz, 1 H), 6.92 (m, 1 H), 4.84 (dd, J = 10.2, 6.2 Hz, 1H), 4.09 (m, 3 H), 3.34 (d, J = 15.5 Hz, 1 H), 3.03 (m, 1 H), 2.18 (m, 2 H), 2.07 (m, 1 H), 2.01 (s, 3 H), 1.65 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 169.4, 150.8 (dd, J = 249.4, 13.2 Hz), 148.1 (dd, J = 246.7, 12.8 Hz), 132.4 (d, J = 12.0 Hz), 124.7 (dd, J = 7.2, 4.9 Hz), 124.2 (q, J = 280.7 Hz), 122.4 (t, J = 3.3 Hz), 116.0 (d, J = 17.0 Hz), 54.5, 52.2, 48.9 (q,. J = 33.8 Hz), 38.4, 33.9, 31.9, 23.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.2, −137.2 (d, J = 22.5 Hz), −143.2 (d, J = 22.5 Hz). Anal. Calcd for $C_{16}H_{17}F_5N_2O_2$: C, 52.75; H, 4.70; N, 7.69. Found: C, 52.81; H, 4.25; N, 7.69.

(*S*)-Isopropyl 2-acetamido-6-amino-5-(2,3-difluorophenyl)-hexanoate (42). The ratio of the two isomers was about 2:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (m, 2 H), 6.90 (m, 1 H), 6.17 (d, J = 7.6 Hz, 1 H), 4.98 (m, 1 H), 4.53 (m, 1 H of the major isomer), 4.47 (m, 1 H of the minor isomer), 2.83−3.05 (m, 3 H), 1.99 (s, 3 H of the major isomer), 1.83 (m, 3 H of the major isomer), 1.83−1.42 (m, 4 H), 1.23−1.15 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (major isomer), 172.0 (minor isomer), 170.0 (major isomer), 169.8 (minor isomer), 150.9 (dd, J = 248.5, 13.5 Hz), 149.6 (dd, J = 246.3, 12.8 Hz, major isomer), 149.5 (dd, J = 245.7, 12.6 Hz, minor isomer), 132. Two (d, J = 11.3 Hz), 124.4 (m), 123.5 (t, J = 3.5 Hz, major isomer), 123.3 (t, J = 3.4 Hz, minor isomer), 115.5 (d, J = 16.9 Hz), 69.4, 52.4 (minor isomer), 52.0 (major isomer), 47.0 (major isomer), 46.8 (minor isomer), 42.8 (major isomer), 42.7 (minor isomer), 23.35 (major isomer), 23.30 (minor isomer), 21.8 (major isomer), 21.7 (minor isomer). ^{19}F NMR (376 MHz, $CDCl_3$): major isomer δ −137.87 (d, J = 21.1 Hz), −143.1 (d, J = 21.1 Hz); minor isomer δ −137.89 (d, J = 21.1 Hz), −143.4 (d, J = 21.1 Hz).

(3*R*,6*S*)-3-Amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)-azepan-2-one Hydrochloride Methyl *tert*-Butyl Ether Solvate (2). To a suspension of acetamide **46** (800 g, 2.2 mol) in *i*-PrOH (1.2 L) were added H_2O (2.96 L) and 37 wt % hydrochloric acid (758 g, 7.7 mol). The vessel was closed and pressurized with nitrogen (25 psi). The resulting mixture was heated to 95 °C for 17 h until ≥ 99% conversion was achieved. The reaction mixture was cooled to 50 °C, diluted with *i*-PrOH (1.2 L), and further cooled to ambient temperature. Aqueous NaOH (5 N, 2.2 L, 11 mol) was added, maintaining the batch temperature below 30 °C. The reaction mixture was extracted with MTBE (4 L). The organic layer was washed with 0.2 N NaOH (2.4 L) followed by H_2O (2.4 L). The organic phase was solvent switched to *i*-PrOH in vacuo azeotropically to a final volume of 5 L with 1−0.3 wt % water. MTBE (960 mL) followed by 2.56 N HCl in aq *i*-PrOH (0.24 mol, 94 mL; prepared by diluting 212 mL of 37 wt % HCl with *i*-PrOH to 1 L) was added at 30 °C. The resulting solution was seeded with caprolactam HCl salt MTBE solvate **2** (26 g) and aged at 30 °C for 1 h. More 2.56 N HCl in aq *i*-PrOH (2.29 mol, 894 mL; see above for the preparation) was added dropwise at 30 °C over 4 h. After addition, the batch was cooled to ambient temperature over 1 h and aged for 3 h before filtration. The wet cake was washed with 30% MTBE/*i*-PrOH (1.8 L, displacement wash) followed by MTBE wash (2.5 L × 2). Vacuum drying under nitrogen at < 25 °C afforded 840 g of caprolactam HCl salt MTBE solvate **2** as a white solid in 83% yield with 99.9% purity and 100% ee. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.57 (s, 3 H), 7.32 (m, 1 H), 7.22 (m, 2 H), 4.69 (d, J = 11.2 Hz, 1 H), 4.46 (m, 1 H), 4.39 (m, 1 H), 4.20 (m, 1 H), 3.39 (d, J = 15.4 Hz, 1 H), 3.07 (s, 3 H),, 3.06 (m, 1 H), 2.18 (m, 1 H), 2.07 (m, 1 H), 1.99 (m, 1 H), 1.74 (m, 1 H), 1.10 (s, 9 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 171.4, 149.7 (dd, J = 246.2, 13.5 Hz), 146.9 (dd, J = 244.3, 12.8 Hz), 133.1 (d, J = 11.7 Hz), 125.1 (dd, J = 4.7, 7.4 Hz), 124.7 (q, J = 280.5 Hz), 123.4 (t, J = 2.9 Hz), 115.5 (d, J = 16.7 Hz), 72.0, 52.6, 51.8, 48.7, 47.8 (q, J = 32.5 Hz), 36.6, 33.0, 28.4, 26.8. Anal. Calcd for $C_{19}H_{28}ClF_5N_2O_2$: C, 51.07; H, 6.32; N, 6.27. Found: C, 50.82; H, 6.28; N, 6.27.

Telcagepant Potassium Salt Ethanol Solvate (1). Telcagepant was prepared by treating caprolactam **2** with CDI followed by **3** in the presence of Et_3N in THF as reported previously.[5,8,9] Upon workup, the crude reaction stream in *i*-PrOAc was solvent switched to EtOH in vacuo and treated with a solution prepared by dissolving KOBu-*t* in EtOH (1.3 equiv, 16 wt %) to afford telcagepant as its crystalline potassium salt ethanol solvate in 92% yield with > 99.9% purity and > 99.9% ee. ^{1}H NMR (400 MHz, d_4-MeOH): δ 7.75 (dd, J = 5.3, 1.4 Hz, 1 H), 7.38 (dd, J = 7.6, 1.4 Hz, 1 H), 7.15 (m, 3 H), 6.70 (dd, J = 7.6, 5.3 Hz, 1 H), 4.85 (d, J = 11.4 Hz, 1 H), 4.55 (m, 1 H), 4.45 (dq, J = 15.4, 9.5 Hz, 1 H), 4.27 (m, 3 H), 4.05 (dq, J = 15.4, 9.0 Hz, 1 H), 3.61 (q, J = 7.1 Hz, 2 H), 3.46 (d, J = 15.4 Hz, 1 H), 3.16 (m, 1 H), 3.0 (m, 2 H), 2.42 (dq, J = 12.7, 4.4 Hz, 1 H), 2.27 (dq, J = 12.7, 4.4 Hz, 1 H), 2.16 (m, 3 H), 1.81 (m, 3 H). 1.18 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, d_4-MeOH): δ 176.8, 166.1, 159.3, 157.4, 152.1 (dd, J = 246.8, 13.6 Hz), 149.4 (dd, J = 245.1, 13.1 Hz), 139.2, 134.7 (d, J = 11.9 Hz), 127.7, 126.3 (q, J = 279.7 Hz), 126.2 (dd, J = 7.1, 4.8 Hz), 124.3 (t, J = 3.4 Hz),

116.8 (d, J = 17.1 Hz), 114.5, 113.8, 58.5, 55.3, 55.2, 51.6, 49.9 (q, J = 33.6 Hz), 45.4, 45.3, 39.8, 35.9, 32.7, 30.74, 30.72, 18.5.

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Supporting Information Available: Experimental procedure, additional detailed information on mechanism discussion, reaction condition optimization and screening. This material is available free of charge via the Internet at http://pubs.acs.org.