Organic Process Research & Development

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Process Research for Multikilogram Production of Etamicastat: A Novel Dopamine β-Hydroxylase Inhibitor

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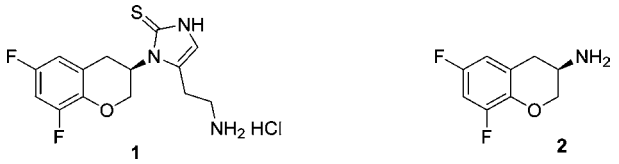
ABSTRACT: In order to develop a manufacturing route to etamicastat, three synthetic approaches to the pivotal chiral 3-aminochroman intermediate have been studied as well as four methods for the construction of the 2-aminoethyl imidazolethione fragment. The evolution of the synthetic strategy based on the early discovery route was described. By focusing on the use of readily available starting materials it was possible to avoid chromatography steps and expensive reagents, bringing about significant improvements in cost and throughput. The best route involves construction of the chiral centre by asymmetric hydrogenation.

INTRODUCTION

Etamicastat (BIA 5-453 or (*R*)-5-(2-aminoethyl)-1-(6,8-difluorochroman-3-yl)-1,3-dihydroimidazole-2-thione hydrochloride, **1**) (Chart 1) is a novel peripherally selective dopamine β-hydroxylase (DBH) inhibitor being developed by Bial-Portela and C[a], S.A. for treatment of hypertension and congestive heart failure.[1] The compound was shown to be well tolerated in healthy volunteers.[2]

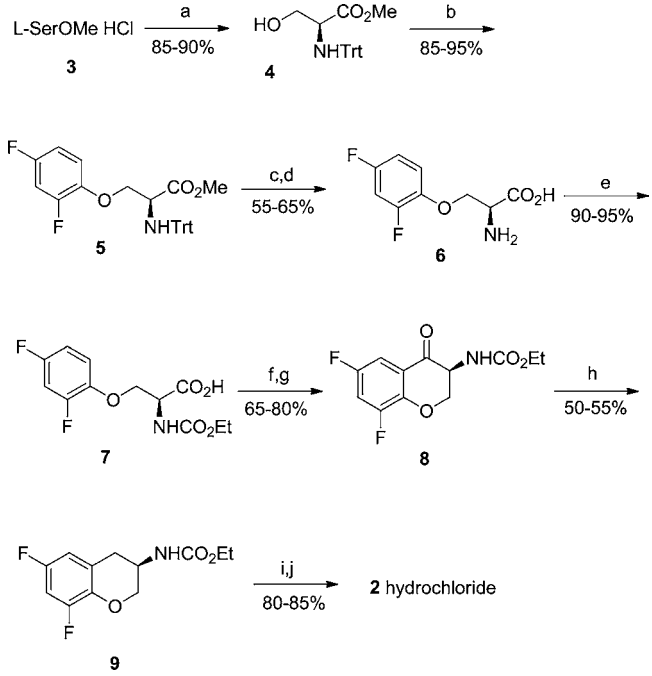
Chart 1



An important part of etamicastat structure is (*R*)-3-amino-6,8-difluorochroman (**2**) (Chart 1) which is also an intermediate in all known syntheses of the drug. In the original medicinal chemistry route,[3] the amine **2** was synthesized starting from L-serine methyl ester hydrochloride (**3**) by condensation of its *N*-trityl derivative (**4**) with 2,4-difluorophenol under Mitsunobu conditions,[4] followed by deprotection of the adduct (**5**), ethoxycarbonylation of the resulting amino acid (**6**), Friedel–Crafts cyclization[5] of N-protected derivative (**7**) and reduction[6] of the ethoxycarbonylamino ketone (**8**). The alkaline hydrolysis of ethyl carbamate (**9**) gave amine **2**, which was isolated as the hydrochloride salt (Scheme 1).

To form the 5-(2-aminoethyl)-1,3-dihydroimidazole-2-thione moiety in the original route, the *tert*-butyl 4-(*tert*-butyldimethylsilyloxy)-3-oxobutylcarbamate (**13**) building block was prepared starting from the known amino diol (**10**),[7] and then reacted with amine **2** and potassium thiocyanate in ethyl acetate in the presence of acetic acid. Under the conditions employed for cleavage of the Boc group (1 N HCl/EtOAc) in the resulting hexahydropyrrolo[2,3-*d*]imidazole-2-thione derivative **14**, simultaneous opening of the pyrrolidine ring occurred to give the target compound **1** (Scheme 2).

Scheme 1. Medchem route to amine 2[a]



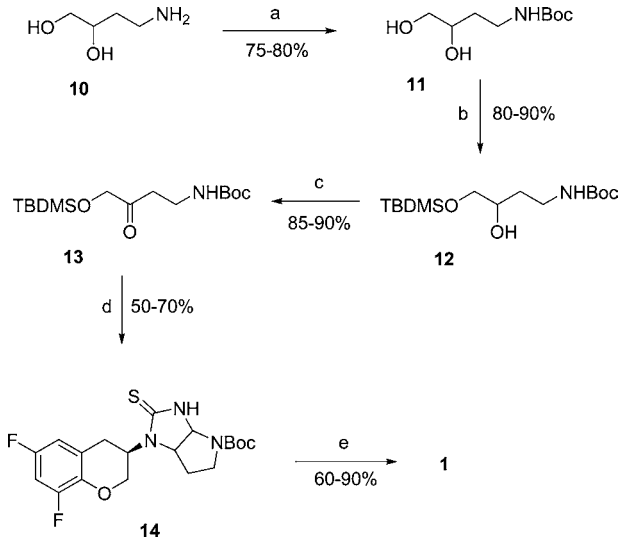
[a]Reagents and conditions: a) Trt-Cl, Et_3N, DMF, rt, 16 h; b) 2,4-difluorophenol, Ph_3P, DEAD, benzene, rt, 2 h; c) 1.4 N HCl in EtOAc, rt, 1 h; d) 1 N NaOH, MeOH, rt, 4 h; e) ethyl chloroformate, NaOH, water, 0–5 °C, 1 h; f) PCl_5, DCM, 0–5 °C, 1 h; g) $AlCl_3$, DCM, 3–8 °C, 4 h; h) 100 psi H_2, Pearlman's catalyst, H_2SO_4, CF_3COOH, rt, 24 h; i) 40% KOH, MeOH, reflux, 24 h; j) 2-propanol, conc HCl, rt.

Part of the medicinal chemistry route (including preparation of intermediates **2** and **13**), and the cyclocondensation reaction suffer from various technological drawbacks, which make the process less convenient for scale-up. For example, intermediates **5** and **12**–**14** are noncrystalline and require chromatographic purification, the reaction medium used for reduction of ketone

Received: January 16, 2012
Published: March 1, 2012

dx.doi.org/10.1021/op300012d | *Org. Process Res. Dev.* 2012, 16, 704–709

Scheme 2. Medchem synthesis of etamicastat[a]



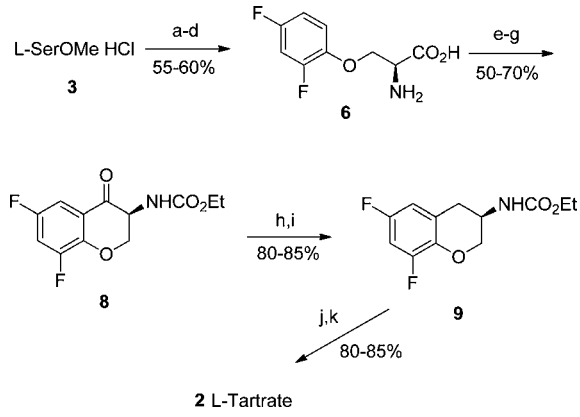
[a]Reagents and conditions: a) Boc_2O, EtOH, rt, 2 h; b) TBDMS-Cl, Et_3N, DMAP, DCM, rt, 18 h; c) Dess–Martin periodinane, DCM, rt, 1 h; d) **2**, KSCN, AcOH, EtOAc, reflux, 7 h; e) 2 N HCl, EtOAc, rt, 2 h.

8 (mixture of trifluoroacetic and sulfuric acids[6]) is very corrosive, and the yield obtained in this step is low. It was therefore necessary to optimize the existing scheme or develop an alternative approach to prepare kilogram quantities of etamicastat to supply clinical trials.

DEVELOPMENT OF SYNTHETIC ROUTES TO (*R*)-3-AMINO-6,8-DIFLUOROCHROMAN (2)

Initial efforts were directed to optimization of the route depicted in Scheme 1. Preparation of the difluorochroman **2** was lengthy, and several unit operations were required. After some familiarization with the process, it was found that isolation of *N*-trityl derivative (**4**) was not necessary if the tritylation solvent was changed from DMF to dichloromethane. Telescoping to amino acid **6** was successfully achieved by avoiding chromatographic purification of the Mitsunobu reaction and directly performing a biphasic hydrolysis of the reaction mixture followed by isolation of the amino acid **6** from the aqueous layer after neutralization. N-Protected amino acid (**7**) could also be telescoped to the Friedel–Crafts cyclization step in DCM solution without isolation. One difficult task appeared to be optimization of reduction of the ketone **8**. Reduction of aryl ketones (such as compound **8**) to methylene compounds (such as compound **9**) is a synthetically useful reaction, and various methods have been developed for this transformation, namely Clemmensen and Wolff–Kishner reductions, catalytic hydrogenolysis,[8−10] Et_3SiH/CF_3COOH,[9,10] $Et_3SiH/BF_3{\cdot}Et_2O$,[10] $Et_3SiH/TiCl_4$,[11] $NaBH_4/BF_3{\cdot}Et_2O$.[12] However, in our experiments none of the above methods proved to be efficient for the conversion of **8** to **9**, yielding the intermediate alcohol or its mixture with the starting material. Attempts to reduce the intermediate alcohol to **9** with other reagents known to be efficient for this kind of transformation, such as iodotrimethylsilane[13] or its equivalents[14] did not work either. A screening of different solvent–acid combinations for catalytic hydrogenolysis over Pd/C was performed, and surprisingly, it was found that carrying out the reduction in a mixture of 3 volumes of dichloromethane and 1 volume of methanesulfonic acid gave complete conversion of **8** to **9**. However, the analysis of the optical purity of compound **9** revealed significant racemization. The racemization was attributed to the enantiomeric instability of the starting compound **8** in the reaction mixture. To overcome the racemization issue, a two-step method, comprising the conversion of **8** to the intermediate alcohol with sodium borohydride in methanol followed by catalytic reduction in the dichloromethane–methanesulfonic acid mixture, was investigated. At laboratory scale, the two-step process reproducibly gave high yield of compound **9** with 94–99% ee. This was successfully demonstrated in the first kilo batches at 5-kg scale. It was then decided to produce the first pilot batches, and when the reaction was carried out on 100-kg scale, some racemization was noticed both for the Friedel–Crafts cyclization and reduction steps. Compound **9** was obtained with unexpectedly lower enantioselectivity of 80% ee. Isolation of compound **2** as the L-tartrate salt upgraded the optical purity to the required 98% ee. An overview of the L-serine route to compound **2** that was taken to the pilot scale is depicted in Scheme 3[15]

Scheme 3. Optimized L-serine route to (*R*)-3-amino-6,8-difluorochroman (2)[a]



[a]Reagents and conditions: a) Trt-Cl, Et_3N, DCM, rt, 6 h; b) 2,4-difluorophenol, Ph_3P, DIAD, toluene, 25–30 °C, 4 h; c) 6 N HCl, reflux, 1 h; d) 32% NaOH, water, rt; e) ethyl chloroformate, NaOH, water, 0–5 °C, 1 h; f) PCl_5, DCM, 0–5 °C, 3 h; g) $AlCl_3$, DCM, 3–8 °C, 6 h; h) $NaBH_4$, MeOH, 5–10 °C, 30 min; i) 100 psi H_2, 10% Pd/C, MSA, DCM, rt, 7 h; j) 40% KOH, MeOH, reflux, 24 h; k) L-tartaric acid, ethanol, water, rt, 1 h.

Although the optimized L-serine route allowed the preparation of multikilogram quantities of compound **2**, due to the relatively high cost of starting materials, moderate yields, and more importantly, configurational instability of the protected amino ketone **8** on scale, the process required further optimization for commercial production.

After the L-serine route, another alternative synthetic pathway, employing asymmetric hydrogenation of a corresponding ene-carbamate as a chiral center-forming step, was developed. Ene-carbamates **19** were prepared on laboratory scale starting from 2,4-difluorophenol **15** by formylation with hexamethylenetetramine in trifluoroacetic acid to aldehyde **16**, and subsequent cyclization with acrylonitrile in the presence of DABCO to afford nitrile **17**. Alkaline hydrolysis of **17**, followed by the Curtius rearrangement of the corresponding acyl azide in the appropriate alcohol or alcohol–toluene mixture, gave the requisite ene-carbamates **19** (Scheme 4).[16] For asymmetric

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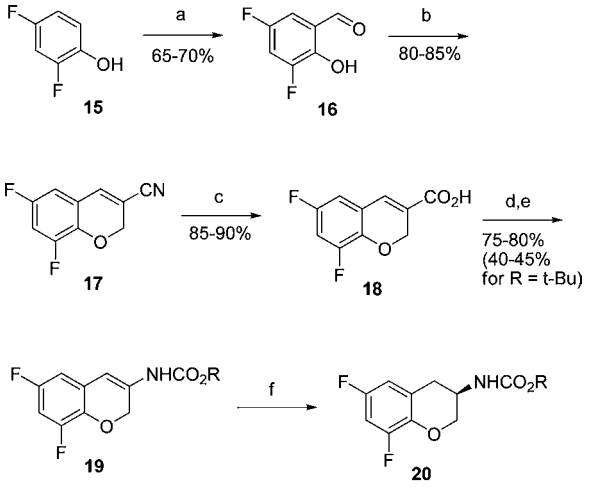
Scheme 4. Synthesis of carbamates 20 via Curtius reaction[a]

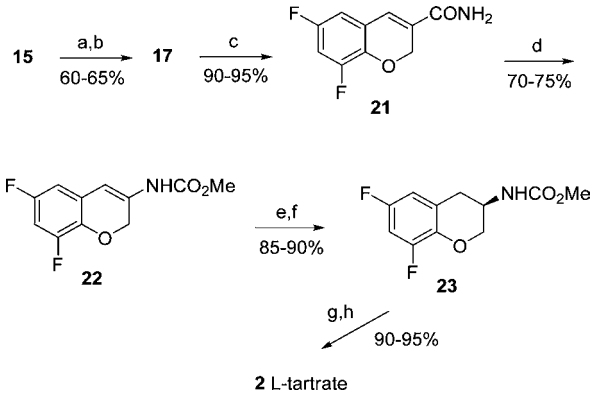


[a]Reagents and conditions: a) HMTA, CF_3COOH, 115 °C, 18 h; b) CH_2═CHCN, DABCO, reflux, 16 h; c) NaOH, water, reflux, 4 h; d) DPPA, Et_3N, acetone, 15 °C, 2 h; e) ROH or ROH−toluene, 60−100 °C, 3−5 h; f) Ru biphosphine catalyst S/C 100, 30 bar H_2, MeOH, 60 °C, 20 h.

hydrogenation of **19**, the catalyst screening program was initially performed with a S/C ratio 100 using a preformed Ru or Rh catalyst in methanol at 30 bar H_2 and at 60 °C for 20 h. Conversion and ee were followed by chiral HPLC. The best hydrogenation results (full conversion at 90−95% ee) were obtained with methyl carbamate (**19**, R = Me) in conjunction with Ru complexes of (*R*)-Xyl-P-Phos,[17] CatASium T3,[18] (*R*)-C3-TunePhos[19] and (*R*)-TolBINAP[20] ligands. Early studies showed that the presence of phosphoric acid was beneficial to the reaction with respect to conversion and ee.

After completion of the asymmetric hydrogenation proof of concept, further optimization of both the ene-carbamate substrate preparation method and the reduction step was undertaken. It was found that the presence of water was not detrimental for the cyclocondensation of aldehyde **16** and acrylonitrile which allowed taking the water-wet cake of **16** to the next step, thus avoiding drying of the volatile product (Scheme 5). The acrylonitrile (suspected carcinogen) that was used in high quantities as a reagent and solvent was largely replaced by a DMF−water mixture, thus minimizing the safety risk and facilitating isolation of the nitrile **17** (by crystallization upon cooling). As the use of azide chemistry may be undesirable at scale, a modified procedure that allowed a safer method and was more amenable to larger-scale production was investigated. A suitable alternative procedure was devised using the Hofmann rearrangement of carboxamide (**21**) (which was prepared by the acidic hydrolysis of nitrile (**17**)[16]) affording the methyl ene-carbamate (**22**) in comparable yield. An exhaustive optimization of conditions for the asymmetric reduction of ene-carbamate **22** allowed the S/C ratio to be increased to 4000:1 without loss of enantioselectivity or conversion. Recrystallization of crude carbamate (**23**, 92% ee) from aqueous 2-propanol efficiently removed unwanted enantiomer, affording **23** with 98% ee in high yield. Alkaline hydrolysis of methyl carbamate **23** was performed in a way

Scheme 5. Optimized route to (*R*)-3-amino-6,8-difluorochroman (2) via asymmetric reduction of ene-carbamate 22[a]



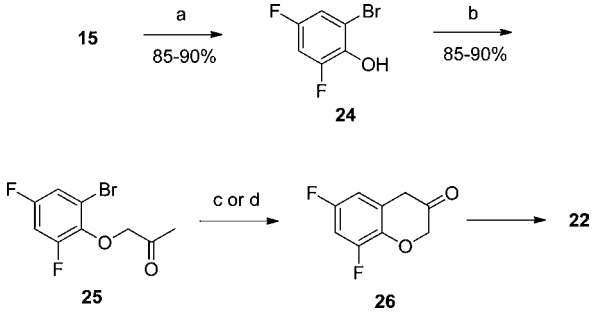
[a]Reagents and conditions: a) HMTA, CF_3COOH, 115 °C, 18 h; b) CH_2═CHCN, DABCO, DMF, water, 70 °C, 16 h; c) H_2SO_4, AcOH, 100 °C, 1 h; d) NaClO, NaOH, MeOH, 25 °C, 24 h; e) Ru biphosphine catalyst S/C 4000, 30 bar H_2, MeOH, 80 °C, 20 h; f) water, 2-propanol, reflux to 20 °C; g) 40% KOH, MeOH, reflux, 24 h; h) L-tartaric acid, ethanol, water, rt, 1 h.

similar to that of the cleavage of ethyl carbamate **9**, resulting in the amine **2** with 99% ee (Scheme 5).

After performing the first kilo batches (5-kg scale), the process was considered suitable for further scale-up. Several 100-kg scale batches of the amine **2** L-tartrate were produced, yielding product that was within chemical and optical purity specifications. From the point to view of waste generation, the optimization work carried out in the ene-carbamate route led to a significant reduction in waste. The reduction was about 20% when compared to optimized L-serine route.

Although the process was shown to be scalable and robust, alternative routes to ene-carbamate **22** were evaluated at the same time in order to further increase cost efficiency of the method. One of the strategies focused on an intramolecular version of Pd-catalyzed α-arylation of aliphatic ketones,[21] which was expected to produce 3-chromanone **26** from methyl ketone **25** (Scheme 6). Bromination of 2,4-difluorophenol (**15**) proceeded smoothly, as described,[22] to give bromo phenol **24**, and alkylation of the latter with chloroacetone produced ketone **25** in high yield. Unfortunately, cyclization of **25** to **26**

Scheme 6. Route to ene-carbamate 22 via intramolecular α-arylation of aliphatic ketone[a]



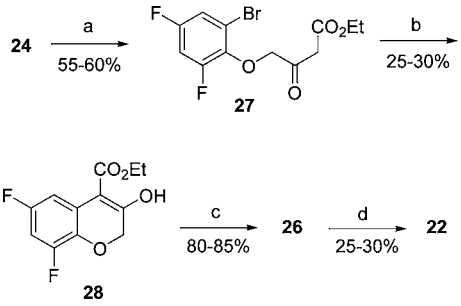
[a]Reagents and conditions: a) Br_2, water, 0−5 °C, 2 h; b) chloroacetone, K_2CO_3, cat. KI, THF, reflux, 4 h; c) Pd complex, base, heating in organic solvent; d) CuI, DMEDA, base, heating in organic solvent.

dx.doi.org/10.1021/op300012d | *Org. Process Res. Dev.* 2012, 16, 704−709

did not achieve the yield required to make this interesting for further development.

Another approach was based on the Cu-catalyzed ring closure of aromatic bromides with 1,3-dicarbonyl moiety[24] which implies the replacement of chloroacetone in Scheme 6 with commercially available and relatively cheap ethyl 4-chloroacetoacetate (Scheme 7). Alkylation of phenol **24** was carried out in DMSO solution in the presence of potassium hydroxide. After chromatographic purification this yielded the adduct **27** as an oil in a moderate yield. The cyclization performed sluggishly, producing the enol form of chromanone **28** in low yield after column chromatography, although the crude reaction mixture contained approximately 80% of the desired product. Hydrolysis of the ester group followed by decarboxylation was performed without isolation of the intermediate acid by refluxing compound **28** in 20% sulfuric acid to give ketone **26**. Conversion of the latter to the target ene-carbamate **22** was achieved according to the published procedure,[24] with >80% yield (crude compound). However, due to formation of many impurities, chromatographic purification became necessary, and the isolated yield was therefore low. However, a direct crystallization from acetic acid/water is sufficient to avoid the chromatography step.

Scheme 7. Route to ene-carbamate 22 via intramolecular α-arylation of 1,3-dicarbonyl derivative[a]



[a]Reagents and conditions: a) ethyl 4-chloroacetoacetate, KOH, DMSO, 20−25 °C, 1.5 h; b) CuI, DMEDA, K_2CO_3, dioxane, reflux, 6.5 h; c) 20% aqueous H_2SO_4, reflux, 16 h; d) *N*-methyl carbamate, *p*-TsOH, toluene, reflux, 1 h.

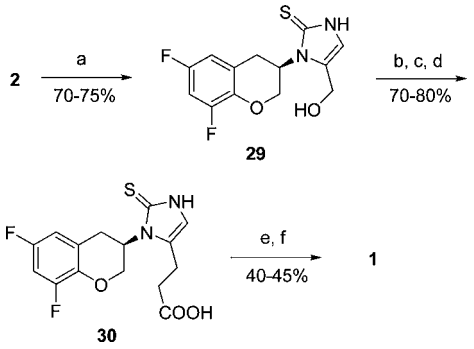
The chemistry depicted in Scheme 7 is feasible and attractive from the cost-of-goods perspective. However, due to low isolated yields seen in several steps, the need for chromatographic purification and noncrystalline intermediate **27**, route optimization is to be considered for Scheme 7.

DEVELOPMENT OF SYNTHETIC ROUTES TO ETAMICASTAT

As has already been mentioned, all studied synthetic routes to etamicastat employed (*R*)-3-amino-6,8-difluorochroman (**2**) as starting material. Initially, the medchem route did not seem convenient for development as all the intermediates were oils. The first tested approach consisted of reacting hydroxymethylimidazole with a C nucleophile via direct displacement of the hydroxy group. Hydroxymethylimidazoles have been shown to react with N-nucleophiles.[6,25] The hydroxymethyl intermediate **29** was prepared by cyclocondensation of **2** with a dihydroxyacetone dimer and potassium thiocyanate in ethyl acetate in the presence of acetic acid (Scheme 8).

We have found that in the presence of sodium ethoxide, diethyl malonate reacted cleanly with compound **29**, affording the corresponding diester (not shown). After hydrolysis and decarboxylation this gave imidazolepropionic acid **30** in high yield.[26] Conversion of the acid **30** to **1** was achieved via a two-step Curtius process involving isolation of the intermediate acyl azide to give an overall yield of 40−45%. All attempts to perform the reaction without isolation of the azide or to use alternative azide-free processes (Hofmann or Schmidt reactions) were unsuccessful.

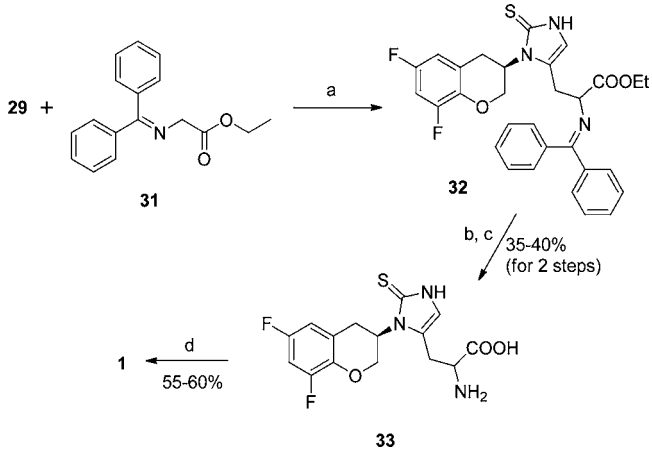
Scheme 8. Synthesis of 1 via malonate addition to hydroxymethylimidazole 29[a]



[a]Reagents and conditions: a) dihydroxyacetone dimer, KSCN, AcOH, EtOAc, 50 °C, 2 h; b) diethyl malonate, EtONa, EtOH, 20−25 °C, 16 h; c) NaOH, water, MeOH, 20−25 °C, 4 h; d) HCOOH, Et_3N, 115 °C, 2 h; e) DPPA, Et_3N, EtOAc, 0−5 °C, 4.5 h; f) 1N HCl, HCOOH, dioxane, 60−75 °C, 1.5 h.

A subsequent development of the above approach was an attempt to use a malonate analogue with the amino group incorporated in the correct position for the reaction with **29**. Among several tested glycine derivatives, condensation with the benzophenone imine **31** in THF in the presence of potassium *tert*-butoxide was successful (Scheme 9). The primary adduct **32** was fully deprotected without isolation to give crystalline amino acid **33** as a mixture of diastereomers in moderate yield. Decarboxylation of **33** occurred in refluxing cyclohexanol (156 °C) although 2-cyclohexen-1-one was required as a catalyst.[27] Due to harsh conditions, the reaction was accompanied by

Scheme 9. Synthesis of 1 via glycinate addition to hydroxymethylimidazole 29[a]



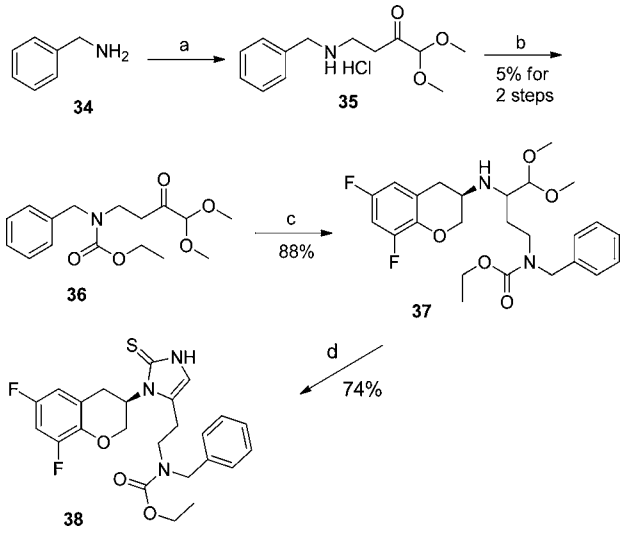
[a]Reagents and conditions: a) t-BuOK, THF, −5−0 °C to 20−25 °C, 3 h; b) LiOH, THF, water, 20−25 °C, 16 h; c) AcOH, distillation of THF and water; d) 2-cyclohexen-1-one, cyclohexanol, reflux, 2 h.

dx.doi.org/10.1021/op300012d | Org. Process Res. Dev. 2012, 16, 704−709

some decomposition, and isolation of the product required chromatographic purification. Compound **1** was produced in moderate yield.

Yet another tested approach towards the construction of imidazolethione moiety is shown in Scheme 10. Dimethoxy

Scheme 10. Route to 1 via protected α-amino aldehyde 37[a]



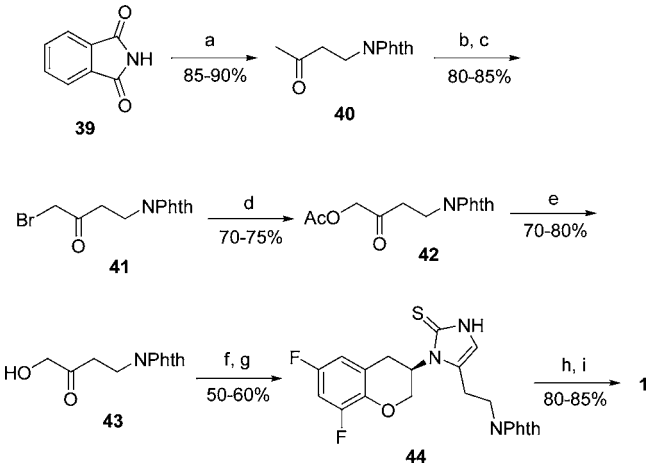
[a]Reagents and conditions: a) 1,1-dimethoxyacetone, HCHO, HCl, water, reflux, 4 h; b) ethyl chloroformate, Et_3N, MeOH, 20−25 °C, 2 h; c) compound **2**, STAB-H, DCM, 20−25 °C, 4 h; d) KSCN, 1 N HCl, EtOH, reflux, 5 h.

ketone **36** was used as a model substrate for reductive alkylation of amine **2** to produce protected α-amino aldehyde **37**. Cyclocondensation of the latter with potassium thiocyanate afforded the desired imidazolethione **38** in reasonable yield. However, the route was not further developed as no convenient synthetic method for N-protected 4-amino-1,1-dimethoxybutan-2-one was available. For example, ketone **36** was prepared by Mannich reaction of benzylamine (**34**) followed by ethoxycarbonylation of intermediate **35** of an overall yield of only 5%.

Finally, the medchem route (Scheme 2) was reassessed in order to find suitably protected 4-amino-1-hydroxybutan-2-one (analogue of ketone **13**) to be used in the cyclocondensation reaction with amine **2** and thiocyanate. To be amenable to larger-scale preparation, the intermediate needs to be readily available, crystalline, and able to give cyclization product that crystallizes easily. After an extensive study of various protecting groups, the phthalimido hydroxy ketone **43** was selected (Scheme 11).[28]

The hydroxy ketone **43** was prepared using standard chemistry by Michael addition of methyl vinyl ketone to phthalimide (**39**), selective bromination of ketone **40** in methanol,[29] conversion of bromide **41** to acetoxy derivative **42** and finally acidic hydrolysis of the latter. The bromination reaction of compound **40** was assessed with other reagents to avoid the use of bromine due to its toxic properties. Reagents such as N-bromosuccinimide or 5,5-dimethyl-1,3-dibromohydantoin failed to generate the desired product. Calorimetric studies on the bromination reaction were carried out (RC1 and DSC), and it was found that ΔT (adiabatic) is 22 °C. A second exotherm was also observed because of product crystallization during reaction. This was overcome on scale by charging

Scheme 11. Large-scale route to etamicastat 1[a]



[a]Reagents and conditions: a) methyl vinyl ketone, t-BuONa, EtOAc, EtOH, 40−50 °C, 2−3 h; b) Br_2, MeOH, 20−25 °C, 5 h; c) water, reflux, 1 h; d) KOH, AcOH, reflux, 1 h; e) HCl, water, 2-propanol, 75 °C, 4 h; f) compound **2** L-tartrate, KSCN, AcOH, 100 °C, 2−4 h; g) recryst. from 2-propanol/DCM; h) $NaBH_4$, 2-propanol, DCM, water, 20−25 °C, 16 h; i) HCl, 2-propanol, water, reflux, 1−2 h.

bromine during 8 h which allowed a controlled heat release. Compound **43** is a stable crystalline material which can be recrystallized from 2-propanol. The above chemical route allowed for its preparation in good yield with 99% purity. Cyclocondensation of ketone **43** with the L-tartate of amine **2** and potassium thiocyanate was performed in acetic acid at 100 °C. The target imidazolethione **44** cocrystallized with potassium tartrate upon dilution of the reaction mixture with water and cooling. The tartrate salt was then removed by recrystallization from 2-propanol−DCM. Because of a moderate yield on the cyclization step, an extensive optimization work was performed. However, neither alteration of the ratio of reagents nor fine-tuning of the reaction parameters increased the yield. Removal of the phthalyl-protecting group was performed using a modified sodium borohydride method[30] and produced **1** in high yield and also purity above 99%. A critical parameter in this step was the hydrogen formation and accumulation during the reaction. To avoid the risk of hydrogen accumulation on scale, the addition of sodium borohydride was carried out in steps during a period of 4 h (10-min intervals) whilst maintaining the temperature below 10 °C.

By combining the route in Scheme 11 with the process of amine **2** synthesis (depicted in Scheme 5), the convergent 12-step process was used for industrial scale production of etamicastat (**1**). Three lots of approximately 60 kg each were produced with overall yield 11% starting from difluorophenol, and the product complied with the defined specifications.

■ CONCLUSION

A convergent manufacturing route to etamicastat (**1**) has been developed and scaled up to 60 kg batches. Several synthetic approaches to the pivotal chiral 3-aminochroman intermediate (**2**) were studied using both starting material from the chiral pool and by constructing the chiral center via asymmetric hydrogenation. Several methods for building 2-aminoethyl imidazolethione fragment were tested. The manufacturing route utilizes readily available inexpensive starting materials.

dx.doi.org/10.1021/op300012d | Org. Process Res. Dev. 2012, 16, 704−709

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Notes

The authors declare no competing financial interest.

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