A Flexible, Practical, and Stereoselective Synthesis of Enantiomerically Pure *trans*-5-Oxohexahydropyrrolo[3,2-*b*]pyrroles (Pyrrolidine-*trans*-lactams), a New Class of Serine Protease Inhibitors, Using Acyliminium Methodology

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A flexible, practical, and stereoselective synthesis of enantiomerically pure *trans*-5-oxohexahydropyrrolo[3,2-*b*]pyrroles (pyrrolidine-*trans*-lactams) is described. The key reaction involves addition of *Z*-ketene acetal **24** to the acyliminium ion derived from **48**. This reaction is mediated by BF_3·OEt_2 and introduces the 6*S* and 6a*S* stereocenters stereoselectively. The acyliminium precursor was prepared in four different ways: from racemic 2,4-diaminobutyric acid **8**, from (*R*)-asparagine, from (*R*)-methionine, and *via* a crystallization-induced dynamic resolution of a salt of the racemic amine **56**. (*R*)-Methionine is the preferred starting material for the preparation of enantiomerically pure material. The best conditions for addition of the ketene acetal to the acyliminium ion derived from **48** were determined by systematically screening a range of ketene acetals and Lewis acids. The best ketene acetal was *Z*-(1-ethoxy-3-methylbut-1-enyloxyl)triisopropylsilane **24**. In this series, the bulk of the silyl group of the *Z*-ketene acetal can be correlated with increased 6*S* isopropyl product. Use of the *E*-ketene acetal does not lead to a significant change in stereoselectivity for the 6*R* isopropyl product. In contrast, variation of the Lewis acid has a considerable effect on the product stereochemistry. While BF_3·OEt_2 gives predominantly 6*S*,6a*S* product, $AlCl_3$ and $TiCl_4$ give predominantly mixtures of the 6*R*,6a*S* and 6*S*,6a*S* products and TMSOTf gives 6a*R* material with predominantly one unknown isopropyl isomer (*trans*-lactam numberings used). The synthesis can conveniently be carried out on a large scale to produce multigram quantities of the *trans*-lactam **28**, which is a key precursor of pharmacologically active molecules such as **1**, a selective and orally active human neutrophil elastase inhibitor. The overall chemical yield of **1** is 1.3%, corresponding to an average of >70% yield for each of the 14 steps, and the synthesis contains only one chromatographic purification.

Introduction

Serine proteases constitute a major class of enzymes that are widely distributed in the human body and are frequently implicated in life-threatening disease states. Consequently, enormous research programs, many within the pharmaceutical industry, are targeted at identifying selective serine protease inhibitors. Despite these efforts, there are only a few simple, tractable nonpeptidic templates for serine protease inhibition. However, research at GlaxoWellcome has recently identified new templates based on 5,5-*trans*-fused ring systems[1]—including pyrrolidine-*trans*-lactones[2] and pyrrolidine-*trans*-lactams[2]—which possess inhibitory activity against serine proteases such as trypsin, chymotrypsin, thrombin, and cathepsin G.[2] The discovery that these templates also provide effective inhibitors of human neutrophil elastase (HNE),[2] combined with the knowledge that such inhibitors are widely considered as potential therapy for respiratory disease,[3] was of interest to us at GlaxoWellcome as part of a long-term search for effective therapies for respiratory diseases that has led to the discovery of bronchodilators such as Ventolin and Serevent used in the treatment of asthma.

In chronic bronchitis, HNE is thought to play a pivotal role in generating the excessive mucorrhea and mucus-secreting cell hyperplasia characteristic of the disease.[4]

† Physical Sciences.

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(2) (a) Macdonald, S. J. F.; Belton, D. J.; Buckley, D. M.; Spooner, J. E.; Anson, M. S.; Harrison, L. A.; Mills, K.; Upton, R. J.; Dowle, M. D.; Smith, R. A.; Molloy, C. R.; Risley, C. *J. Med. Chem.* **1998**, *41*, 3919−3922. (b) Macdonald, S. J. F.; Spooner, J. E.; Dowle, M. D. *Synlett* **1998**, 1375−1377. (c) Macdonald, S. J. F.; Montana, J. G.; Buckley, D. M.; Dowle, M. D. *Synlett* **1998**, 1378−1380. (d) Macdonald, S. J. F.; Mills, K.; Spooner, J. E.; Upton, R. J.; Dowle, M. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3931−3936. (e) Dowle, M. D.; Finch, H.; Harrison, L. A.; Inglis, G. G. A.; Johnson, M. R.; Macdonald, S. J. F.; Shah, P.; Smith, R. A. WO 9736903 A1 971009.

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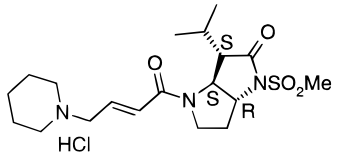
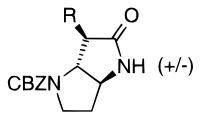
These effects result in recurrent productive cough and lung infection. We believe that inhibitors of HNE may ameliorate these symptoms.

In previous publications,[2] we have described the synthesis and basic medicinal chemistry of some racemic pyrrolidine-*trans*-lactones and lactams. Although potent HNE inhibitors, these compounds were, however, metabolically vulnerable *in vivo*. We have now designed further pyrrolidine-*trans*-lactams that are potent, orally active, and bioavailable in animal models[5] as exemplified by the crotonamido-*trans*-lactam **1**. These compounds have as a template the isopropylpyrrolidine-*trans*-lactam **2**.



1 GW 311616A



2 R = iPr
3 R = ^{n}Pr

A key development in the medicinal chemistry program was the introduction of the isopropyl group in **2** α to the lactam carbonyl and in place of the *n*-propyl group in **3,** which had been present in previous series.[2] This seemingly straightforward structural change remained synthetically elusive for a considerable time. Despite the excellent stereoselectivity of our previous synthesis,[2a] it proved unsuitable as a route for accessing quantities of isopropyl derivatives **2** for our medicinal chemical program. The necessary criteria for alternative syntheses included the following: (i) an efficient route to isopropyl-*trans*-lactams **2**; (ii) the flexibility to introduce a range of alternative groups in place of isopropyl or *n*-propyl; and (iii) the option to prepare large quantities of enantiomerically pure material for drug evaluation if required. Normal scale-up criteria such as high-yielding reactions, the avoidance of low-temperature steps (<−50 °C), or the use of expensive reagents and ease of purification by recrystallization or trituration (rather than chromatography) were also sought. In the long term, these issues would be critical to our ability to efficiently produce quantities of high-purity drug candidate material.

These criteria led to consideration of a synthesis based on acyliminium chemistry. This paper describes our success in using acyliminium chemistry to access either enantiomer of pyrrolidine *trans*-lactams and the development of a robust, flexible, and scalable synthesis. When combined with the ability to use the *trans*-lactams for inhibition of different serine proteases, and with the pedigree that *trans*-lactams can be orally active, bioavailable molecules, it represents a breakthrough that unlocks the enormous potential of this scaffold for exploitation. This is demonstrated by our experience with HNE inhibitors; the chemistry enabled an exploration of a new area of medicinal chemistry that led to a potential lead candidate **1** (GW311616A) and has also laid the foundation for large-scale preparations of pyrrolidine *trans*-lactams.

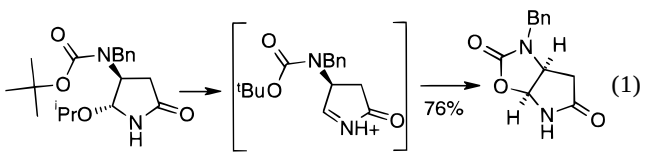
In this paper, we describe (1) the retrosynthetic planning; (2) the construction of the racemic acyliminium ion precursor **15**; (3) the synthesis of a racemic isopropyl pyrrolidine *trans*-lactam **2**; (4) the exploration of the acyliminium chemistry; (5) the preparation of enantiomerically pure isopropyl *trans*-lactam **28**; and (6) the dynamic chiral resolution of a key intermediate **56**.

Retrosynthetic Planning

Previous work in the pyrrolidine *trans*-lactone series[2c] had demonstrated the suitability of acyliminium chemistry to access lactones. We regarded this as good precedent for application to the *trans*-lactam series. Our retrosynthetic plan (Scheme 1) initially disconnected the lactam **2** to the ester **4,** which would be prepared by the reaction of the acyliminium ion **5** with a ketene acetal **6**. We expected from precedent[2c] in our work with the analogous *trans*-lactones to be able to exclusively generate the trans isomer across C-2 and C-3 (as in **4**), and we believed that we would also be able to introduce the isopropyl group stereoselectively by appropriate modification of the ketene acetal **6**. Thus, replacement of the isopropyl group could, in principle, be achieved readily by replacing **6** with a ketene acetal of choice. The acyliminium ion **5** could be accessed from the 3-aminopyrrolidin-2-one **7**, available readily from racemic 2,4-diaminobutyric acid **8**.

Once the validity of this approach had been established, we planned to examine its use in the enantiomerically pure series. In this regard, the configurational stability of the C-3 stereocenter of the acyliminium ion **5** is critical as it controls the generation of the remaining contiguous stereocenters.

There is little literature precedent for the reaction of acyliminium ions containing nitrogen substituents at the 3-position (as in **5**). One example is the reaction of the pyrrolidone **9** where the 3-amino protecting group reacts intramolecularly with the acyliminium ion[6] (eq 1).



9 **10** (1)

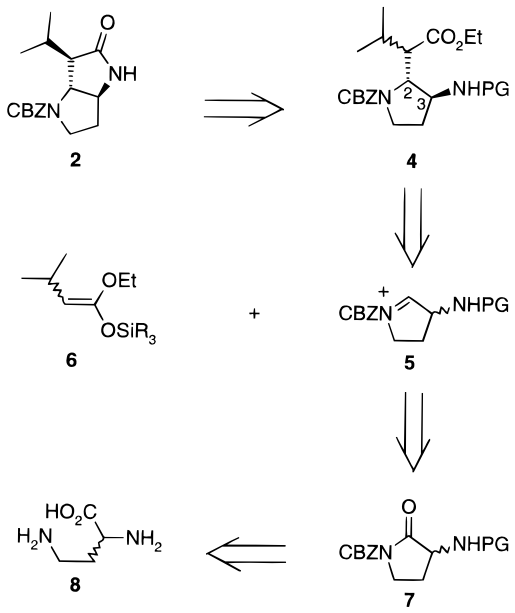
(3) HNE for respiratory diseases: (a) Stockley, R. A. *Am. J. Respir. Crit. Care Med.* **1994**, *150*, S109−S113. (b) Vender, R. L. *J. Invest. Med.* **1996**, *44*, 531−539. Reviews of HNE inhibitors: (c) Hlasta, D. J.; Pagani, E. D. *Ann. Rep. Med. Chem.* **1994**, 195. (d) Edwards, P. D.; Bernstein, P. R. *Med. Res. Rev.* **1994**, *14*, 127. Leading references for HNE inhibitors from pharmaceutical companies and academia follow. Merck: (e) Finke, P. E.; Shah, S. K.; Fletcher, D. S.; Ashe, B. M.; Brause, K. A.; Chandler, G. O.; Dellea, P. S.; Hand, K. M.; Maycock, A. L.; Osinga, D. G.; Underwood, D. J.; Weston, H.; Davies, P.; Doherty, J. B. *J. Med. Chem.* **1995**, *38*, 2449−2462. Zeneca: (f) Veale, C. A.; Bernstein, P. R.; Bohnert, C. M.; Brown, F. J.; Bryant, C.; Damewood, J. R.; Earley, J.; Feeney, S. W.; Edwards, P. D.; Gomes, B.; Hulsizer, J. M.; Kosmider, B. J.; Krell, R. D.; Moore, G.; Salcedo, T. W.; Shaw, A.; Silberstein, D. S.; Steelman, G. B.; Stein, M.; Strimpler, A.; Thomas, R. M.; Vacek, E. P.; Williams, J. C.; Wolanin, D. J.; Woolson, S. *J. Med. Chem.* **1997**, *40*, 3173−3181. Sterling Winthrop: (g) Hlasta, D. J.; Ackermann, J. H.; Court, J. J.; Farrell, R. P.; Johnson, J. A.; Kofron, J. L.; Robinson, D. T.; Talomie, T. G.; Dunlap, R. P.; Franke, C. A. *J. Med. Chem.* **1995**, *38*, 4687−4692. Hoechst: (h) Burkhart, J. P.; Mehdi, S.; Koehl, J. R.; Angelastro, M. R.; Bey, P.; Peet, N. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 63−64. Wichita State University: (i) Kuang, R.; Venkataraman, R.; Ruan, S.; Groutas, W. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 539−544.

(4) (a) Sommeroff, C. P.; Nadel, J. A.; Basbaum, C. B.; Caughey, G. H. *J. Clin. Invest.* **1990**, *85*, 682−689. (b) Thompson, A. B.; Daughton, D.; Robbins, R. A.; Ghafouri, M. A.; Oehlerking, M.; Rennard, S. I. *Am. Rev. Respir. Dis.* **1969**, *140*, 1527−1537.

(5) In-house models were developed by Robin A. Smith and colleagues. Details will be published in due course.

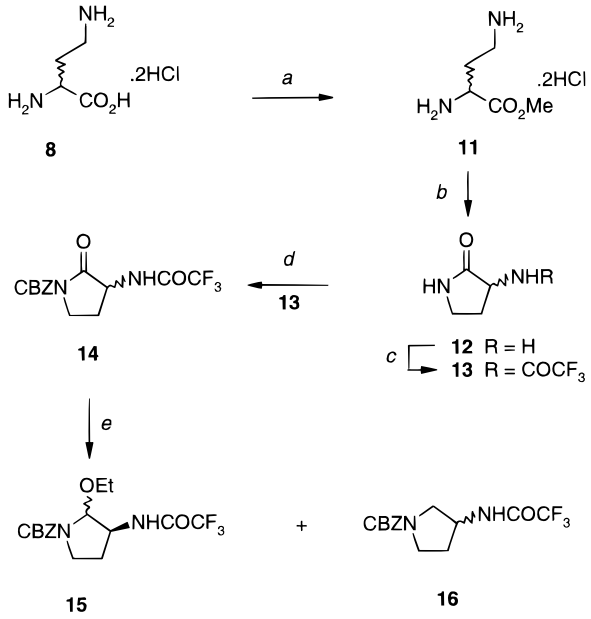
(6) Koot, W.-J.; Hiemstra, H.; Speckamp W. N. *Tetrahedron: Asymmetry* **1993**, *4*, 1941−1948.

Scheme 1[a]



[a] All structures are racemic.

Scheme 2[a,b]



[a] All structures are racemic. [b]Key: (a) AcCl, MeOH, reflux, 95% crude; (b) Dowex 2X8−400 (hydroxide form), MeOH, rt; (c) CF_3CO_2Me, MeOH, rt, 67%; (d) *n*-BuLi, THF, −78 °C, then CBZCl, −70 to −20 °C, 96% crude; (e) $LiBH_4$, THF, −20 °C, then EtOH, cH_2SO_4, 96% crude.

This precedent highlighted the need for the careful selection of nitrogen protecting groups. While recognizing the desirability of the 3-amino protecting group to direct nucleophilic attack at C-2 from the opposite face,[7] we questioned the use of a *tert*-butylcarbamate protecting group (as in **9)** for our purposes, as the acid lability of the *tert*-butyl group may facilitate the observed reaction. Given these criteria, the trifluoroacetyl protecting group was chosen. One concern, however, was the potential lability of the trifluoroacetamide during reduction of the pyrrolidone **7** (PG = $COCF_3$) to a suitable acyliminium precursor.

Construction of the Racemic Acyliminium Precursor 15

The synthesis of the acyliminium precursor **15** starts from commercially available racemic diaminobutyric acid **8** (Scheme 2), which can be converted into the pyrrolidone **12** in one step using hexamethyldisilazane.[8] However, on a larger scale, a two-step procedure was preferred. This involved initially generating the methyl ester **11** under standard conditions and was followed by treatment of the intermediate with Dowex 2 resin (a strongly basic anion exchanger) in methanol. After filtration, the filtrate was reacted with trifluoromethyl acetate to give the crude trifluoroacetamide **13**. Recrystallization from water gave pure **13** in 67% yield.[9] Treatment of this acetamide **13** with 1 equiv of *n*-butyllithium in THF followed by benzyl chloroformate selectively derivatized the lactam nitrogen to give the imide **14** in 96% yield.[10] Exposure of the imide to lithium borohydride in THF[11] resulted in chemoselective reduction of the ring carbonyl to give a mixture of the *cis*- and *trans*-alcohols, which were converted in situ to a 1:1 mixture of *cis*- and *trans*-ethers **15** by addition of ethanol and concentrated sulfuric acid. Addition of the ethanol before the acid suppressed production of **16,** which was otherwise obtained by further reduction. The *cis*- and *trans*-ethers **15** could be separated by flash chromatography to give crystalline solids but were routinely used without purification.

This high-yielding route has been used to produce hundreds of grams of the acyliminium precursor **15** without the requirement for chromatographic purification.

The Synthesis of the Racemic Isopropylpyrrolidine-*trans*-lactam 2

With the availability of the ethers **15**, the scene was set for the key step of the synthesis (Scheme 3, conditions 1). Treatment of either the *cis*- or the *trans*-ether **15** with the commercially available dimethylketene acetal **18** in dichloromethane followed by boron trifluoride at 5 °C provided the *trans* product **19** in 36% yield. This result is consistent with the formation of the acyliminium ion **17** (which is likely to be in equilibrium with the dihydrooxazolium ion as shown in Scheme 3) as the reactive intermediate. ^{1}H NMR experiments (NOE experiments and coupling constants) confirmed the *trans* geometry at C2 and C3 of **19**.[2] Similarly, treatment of **15** with 4:1 *E*/*Z*-isopropyltrimethylsilylketene acetal **20** gave the *trans* products **21** (as confirmed by NOE experiments) with a ratio of isopropyl diastereomers of *ca.* 1.3:1 β/α (as determined by analytical HPLC). (In the racemic

(7) Thaning, M.; Wistrand L.-G. *J. Org. Chem.* **1990**, *55*, 1406−1408 and references therein.

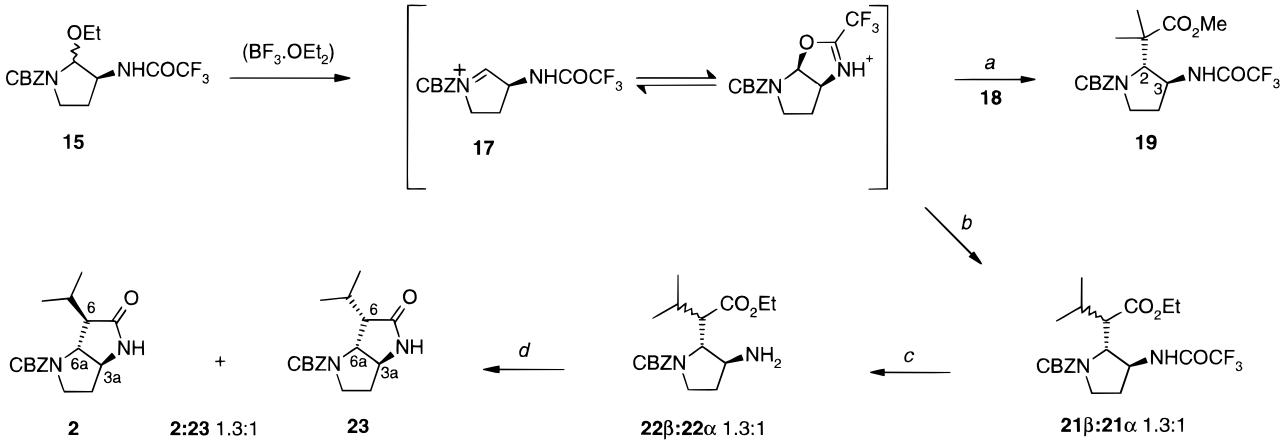
(8) Pellegata, R.; Pinza, M.; Pifferi, G. *Synthesis* **1978**, 614−616.

(9) Recrystallization is important to remove traces of unreacted diaminobutyric acid **8,** which severely affect the efficiency of derivation to the benzyl carbamate **14**.

(10) The lithium salt of **13** is preferred to the sodium salt due to its substantially greater solubility in THF. *n*-Butyllithium is preferred to lithium hexamethyldisilazide to avoid contamination of the product with $CBZNH_2$.

(11) Reduction of the imide **14** can be achieved with $NaBH_4$ and HCl in dioxan. However, excess borohydride is needed, and the reaction is not homogeneous.

Scheme 3[a,b]



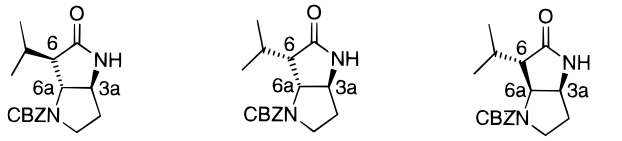
[a] All structures are racemic. [b]Conditions 1 (small scale): (a) $Me_2CC(OMe)OSiMe_3$ **18**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 5 °C to rt, 36%; (b) 4:1 *Z:E*-^{i}PrCHC(OEt)OSiMe$_3$ **20**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 5 °C to rt, (81% if chromatographed); (c) K_2CO_3, H_2O, EtOH, reflux; (d) *t*-BuMgCl, THF, −5 °C, 51% after chromatography for three steps. Conditions 2 (large scale): (b) *Z*-^{i}PrCHC(OSi^{i}Pr$_3$)OEt **24**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 5 °C; (c) K_2CO_3, H_2O, EtOH, reflux; (d) *t*-BuMgCl, 1:1 THF/TMEDA, −5 °C, 20% after recrystallization for three steps.

series as drawn, the β stereochemistry is defined as the isopropyl group drawn up and the α stereochemistry as that drawn down). These isomers can be separated by chromatography, but no purification was actually required at this stage. Instead, removal of the trifluoroacetyl group under basic conditions gave the amines **22**. Lactamization with *tert*-butylmagnesium chloride[12] in THF at −5 °C gave *ca*. a 1.3:1 mixture of the β- and α-isopropyl lactams **2** and **23** in 51% yield for three steps. The relative stereochemistries of **2** and **23** were assigned by ^{1}H NMR experiments. They can be separated by flash chromatography to give *ca*. 1.3:1 **2**β:**23**α, but one recrystallization of the crude material from ethyl acetate gave the more crystalline β-isomer **2** (the desired isomer for our medicinal chemistry program) in analytical purity.

Our confidence in assigning the *trans* ring junction in **2** and **23** from the ^{1}H NMR spectra (vide supra)[2a] was derived from comparison of the coupling constants of the ring junction protons (H6a and H3a) of the *trans*- and *cis*-lactams (whose synthesis is described later) (Table 1). The stereochemistry of the isopropyl groups in **23** and **2** was established by the coupling constants between H-6 and H-6a, which are diagnostic because of the rigidity of these ring systems (Table 1). From decoupling experiments, the β-isopropyl lactam **2** has a coupling of *ca*. 11 Hz (corresponding to an angle between H-6 and H-6a of *ca*. 180°) and the α-lactam **23** has a coupling of *ca*. 6.5 Hz (corresponding to an angle between H-6 and H-6a of *ca*. 30°). Furthermore, these coupling constants for the ring junctions and isopropyl stereochemistry are in good agreement with those predicted by Macromodel and also with those observed for the analogous *trans*- and *cis*-lactones.[2d]

Having established the structures of the β- and α-isopropyl *trans*-lactams **2** and **23**, we wished to establish the stereochemistry of the isopropyl groups in the esters **21**β and **21**α. To this end, the isomers **21**β and **21**α (which had been separated by chromatography) were converted into the respective lactams **2** and **23** by the process just described for the isomer mixture. This allowed the stereochemistry of the isopropyl group for **21**β and **21**α to be assigned. At no point in the conversion of **21**β and **21**α to the respective lactams was the presence of the other isomer detected. Although epimerization of the isopropyl group is in theory possible under the reaction conditions used in these conversions, it is considered unlikely that **21**α would epimerize to give the β-isopropyl lactam **2** and that **21**β would epimerize to give the α-isopropyl lactam **23**.

Table 1. Observed and Predicted[a] Key Coupling Constants for Isopropyl *trans*- and *cis*-Lactams



	2		**23**		**27**[b]	
	obsd	pred	obsd	pred	obsd	pred
J_{6-6a}	11	11.7	6.5	6.8	1	0.7
J_{3a-6a}	10	10.4	10.5	10.5	6	5.8

[a] Predicted values were calculated using Macromodel 6.0, Columbia University, 1996. (Mohamadi, F; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.;. Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440). [b] The predicted coupling contants using Macromodel for the other isopropyl isomer are J_{6-6a} = 5.6 Hz and J_{6a-3a} = 6.3 Hz. The difference in J_{6-6a} between the two isomers and the accuracy of these predicted coupling constants support the assigned stereochemistry of **27**.

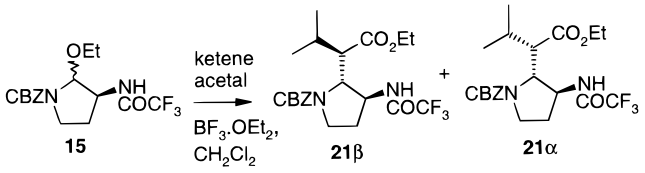
This synthetic route was a breakthrough in our medicinal chemistry program since, for the first time, it allowed us to synthesize a wide variety of β-isopropyl analogues and confirmed, as had been predicted, their superior biological profile over the corresponding *n*-propyl analogues. Although this process generates *ca*. 40% of the undesired α-analogue, the entire synthesis is notable in that *no chromatography is required*.

Exploration of the Acyliminium Chemistry

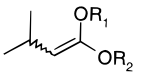
The main drawback of the above synthesis was the production of *ca*. 40% of the undesired α-analogue **23**.

(12) Borthwick, A. D.; Crame, A.; Exall, A.; Mason, A.; Pennell, A. *Tetrahedron Lett*. **1999**, *40*, 3061−2.

Table 2. Reaction of Ketene Acetals with the Acyliminium Precursor 15 (All Structures Racemic)[a]



ketene acetal



R_1	R_2		E/Z ratio	ratio of **21**β/ **21**α
Et	$SiMe_3$	**20**	4:1	1.3:1
Et	Si^tBuMe_2	**25**	1:12.5	3:1
Me	Si^tBuMe_2		1:2	1:1[b]
Me	Si^tBuMe_2		1:10	2:1[b]
Et	Si^iPr_3	**24**	1:12	3.5:1
Et	Si^iBu_3		1:10	2:1
Me	Si^iPr_3		1:12	2.5:1[c]
Et	Si^tBuMe_2		>98:1	1.4:1
Me	$SiEt_3$		unknown	1.4:1

[a] All results unless otherwise stated were obtained by analytical HPLC of a sample of the crude reaction mixtures after dilution with aqueous acetonitrile. [b] These reactions did not proceed to completion. [c] There was also some detrifluoroacetylated product **22** present in the crude reaction mixture.

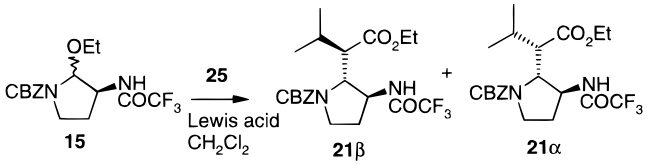
The effect of varying the nature of the ketene acetal and the Lewis acid was investigated in an attempt to improve the β/α ratio in the production of **21**.[13] Given the availability of assigned pure **21**α and **21**β isomers, the β/α ratio of isopropyl esters **21** from crude reaction mixtures under different conditions could be readily determined by analytical HPLC.

A range of ketene acetals were prepared[14] and used in the acyliminium reaction (Table 2).[15] From this limited exploration there appears to be little correlation between the geometry of the double bond of the ketene acetal used and the β/α ratio of the product **21**. However, there is a correlation between the steric influence of the silyl group in the *Z*-ketene acetal and a preference for the β-product **21**β. Thus, a 12:1 mixture of *Z*/*E*-triisopropylsilylketene acetal **24** gave a 3.5:1 ratio of **21**β:**21**α.

We next examined variation of the Lewis acid (and a Bronsted acid) (Table 3) using the 12.5:1 *Z*/*E*-*tert*-butyldimethylsilylketene acetal **25** and found that changing the Lewis acid can alter the β/α ratio. Thus, use of boron trifluoride etherate gave a 3:1 ratio of **21**β:**21**α. In contrast, the use of titanium tetrachloride or aluminum trichloride gave little selectivity for **21**β over **21**α. Formic acid, magnesium(II) bromide, tin(II) triflate, and ytterbium triflate gave no reaction.

Trimethylsilyl triflate did not give the required *trans* products **21**, but instead, cis products **26** with a 6:1 isopropyl stereoisomer ratio in 44% yield were obtained. To confirm the *cis* stereochemistry, the separated isomers were converted into the *cis*-lactams **27** by hydrolysis of the trifluoroacetamide with potassium carbonate in aqueous ethanol (Scheme 4). Both isomers gave only the β isopropyl *cis*-lactam **27**, indicating that one of the isomers had epimerized. ^{1}H NMR experiments confirmed the structure of **27** by observation of an NOE between H6a and H3a and by comparison with the spectra of the *trans*-lactams **2** and **23** (see Table 1).

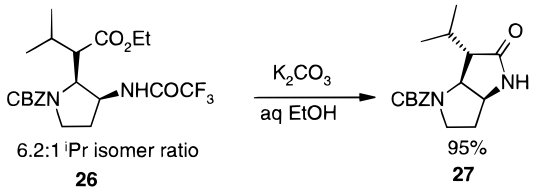
Table 3. Reaction of Acyliminium Precursor 15 (or 48) and the *tert*-Butyldimethylsilylketene Acetal 25 with Lewis Acids (and a Bronsted Acid)



Lewis acid	ratio of **21**β:**21**α[a]	Lewis acid	ratio of **21**β:**21**α[a]
$BF_3{\cdot}OEt_2$	3:1	$Sn(OTf)_2$	no reaction[e]
$TiCl_4$	1:1[b]	$Yb(OTf)_3$	no reaction[e]
$AlCl_3$	1:1[c]	$MgBr_2$	no reaction[e]
HCO_2H	no reaction[d]	TMSOTf	**26** 6:1 isomer ratio[e,f]

[a] The isomer ratios were determined by HPLC analysis of the crude products. [b] The cis isomers across C2−C3 were also produced (3:1 ^{i}Pr isomer ratio); 4:1 **21**:**26**. [c] The cis isomers across C2−C3 were also produced (3:1 ^{i}Pr isomer ratio); 1.3:1 **21**:**26**. [d] The triisopropylsilylketene acetal **24** was used. [e] The homochiral ethers **48** were used instead of **15**. [f] See Scheme 4.

Scheme 4



In contrast with the considerable effort of discovering conditions that would afford predominantly the β isomer, it was with some dismay that we observed that lactamization of **22** with *tert*-butylmagnesium chloride in THF gave a 1:1 mixture of β/α *trans*-lactams **2** and **23**. (This had not previously been observed when lactamizing 1.3:1 **22**β/**22**α). What was also noticed, however, was that with the change in the β/α ratio, benzyl alcohol was also formed in the reaction mixture. It became clear from analytical HPLC of samples taken as the reaction proceeded that the α isopropylamine **22**α was converted into the α isopropyl lactam **23** faster than the β isopropylamine **22**β was converted into the β isopropyl lactam **2**. We postulate that the reaction byproduct, magnesium ethoxide, attacks

(13) We have also explored the use of the boron enolates of isopropyl valerate derivatives attached to a chiral auxiliary (see ref 28).

(14) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877. Oare, D. E.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157−172. Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650−657. Otera, J.; Fujita, Y.; Fukuzumi, S. *Synth. Lett.* **1994**, 213-214.

(15) The (2-cyclopropyl-1-ethoxy-*E*-vinyloxy)trimethylsilane and the (1-ethoxy-2-ethyl-1-butenyloxy)trimethylsilane react with **15** to give the corresponding products in good yield.

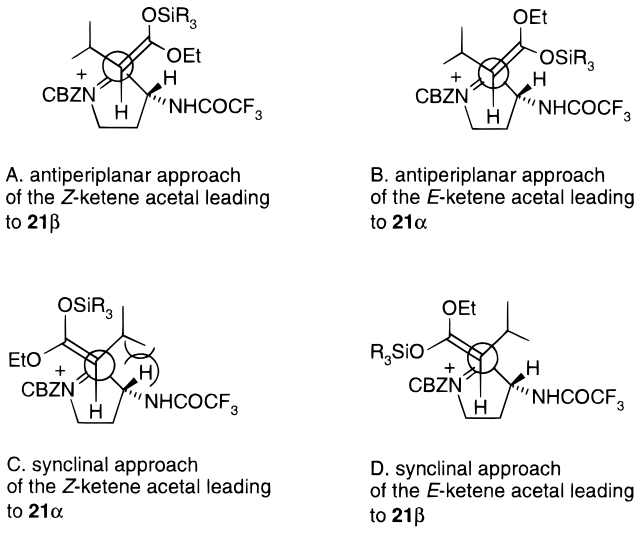


Figure 1.

the benzyl carbamate of either the β isopropylamine **22**β and/or the β isopropyl lactam **2** in preference to the α analogues, leading to a reduction in the yield of the required β isopropyl lactam. This theory was supported by mass spectroscopic evidence showing that ethyl carbamate *trans*-lactam was present in the crude reaction mixture.[16] We reasoned that by adding a metal chelator to the reaction mixture we might reduce the propensity for this side reaction. We were thus gratified to discover that lactamization in a 1:1 mixture of TMEDA/THF[17] preserves the β/α ratio in the lactam products **2** and **23** (although it does not completely suppress benzyl alcohol formation). On a large scale, the desired *trans*-lactam **2** was obtained in 20% yield for three steps from the ethers **15**. This yield is lower when compared with that obtained previously (*vide supra*) and reflects principally loss of material during purification of the lactam **2** by recrystallization (as opposed to chromatography) and loss of the amines **22** during the acid/base workup.

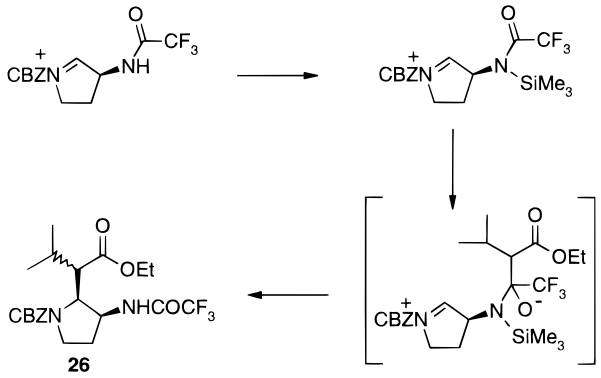
Discussion of the Stereocontrol for the Addition of Ketene Acetals to the Acyliminium Ion Mediated by Different Lewis Acids

Figure 1 shows the antiperiplanar (A and B) and the synclinal (C and D) approaches of the *E*- or *Z*-silylketene acetals to the acyliminium ion. Our results show that either approach of the *E* ketene acetal is approximately equally favored with $BF_3{\cdot}OEt_2$ as the Lewis acid, which presumably indicates that the steric demands of the isopropyl group and the silyloxy group are similar. In contrast, with the *Z*-ketene acetal the antiperiplanar approach is preferred due to reduced interactions between the OEt of the acetal and H3 of the iminium ion (as in A) over the ^{i}Pr of the acetal and H3 of the iminium ion (as in C). Increasing the steric demands of the silyl group leads to restricted rotation of the ^{i}Pr group and a corresponding preference for A.

(16) A typical mass spectrum (thermospray) shows the presence of desired product **23** and **2** − MH^+ 303 (100%) and MNH_4^+ 320 (50%) and peaks consistent with the corresponding ethyl carbamate MH^+ 241 (30%) and MNH_4^+ 258 (5%).

(17) Lactamization using *t*-BuMgCl in Et_2O or solvent mixtures of THF and Et_2O fail to improve the β/α ratio.

Scheme 5



A clue to an alternative or contributing explanation for the observation that *E*-ketene acetals preferentially give β rather than α isopropyl products comes from a serendipitous observation that the *E*-ketene acetal (>98% *E*), on standing in the dark for over a year, had isomerized completely to the *Z*-ketene acetal together with some decomposition to ethyl isovalerate. We cannot therefore rule out the possibility that the *E*-ketene acetals, in the presence of the Lewis acid, isomerize *in situ* to give the *Z*-ketene acetals before reaction with the acyliminium ion. This isomerization of *E*- to *Z*-ketene acetals has been observed by Wilcox[18] with trialkylammmonium perchlorates and by Adam[19] with trifluoromethyl ketones.

Whatever the reason for the *Z*-ketene acetal giving a greater level of stereocontrol over the *E*-ketene acetal, it is clear that the nature of the Lewis acid plays a crucial role. It is not immediately apparent why $BF_3{\cdot}OEt_2$ gives better stereocontrol than $TiCl_4$ or $AlCl_3$, although the labilities of the metal−halogen bonds may be a factor. While the $BF_3{\cdot}OEt_2$-mediated reaction is highly robust and has been repeated many times, the parameters of these reactions in terms of temperature, solvent, stoichiometries (Lewis acid and ketene acetal), and the reaction times in terms of their effect on the stereochemistries of the products are not well understood.

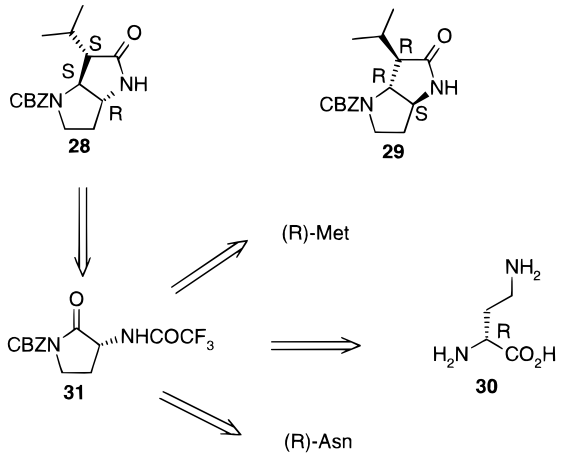
A possible explanation for the TMSOTf-mediated reaction giving only cis products is shown in Scheme 5. After *N*-silylation, the trifluoromethyl acetamide becomes more susceptible to attack by the ketene acetal than the acyliminium ion. This in effect then delivers a tethered nucleophile to the iminium ion from the same face, resulting in cis products. Desilylation occurs in workup.

Application of This Chemistry To Prepare Enantiomerically Pure Isopropyl *trans*-Lactam 28

The capacity to prepare large quantities of isopropyl *trans*-lactam greatly facilitated the discovery of potential drug candidates in our medicinal chemistry program. The next challenge involved the preparation of the enantiomers of these potential drug candidates (such as **1**) to determine their biological profiles and to assign their absolute stereochemistry. We therefore separated the racemic *trans*-lactam **2** into its enantiomers **28** and **29** by preparative HPLC[20] and prepared analogues (such as **1**). We then determined which enantiomer was the more potent inhibitor of HNE, although its absolute stereo-

(18) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451−3.
(19) Adam, W.; Wang, X. *J. Org. Chem.* **1991**, *56*, 7244−50.

Scheme 6



chemistry remained unknown. To address this issue, we decided to investigate whether the acyliminium chemistry described herein could be used to generate enantiomerically pure material. If successful, it would allow assignment of the absolute stereochemistry and also allow access to greater quantities of enantiomerically pure material for further biological evaluation.

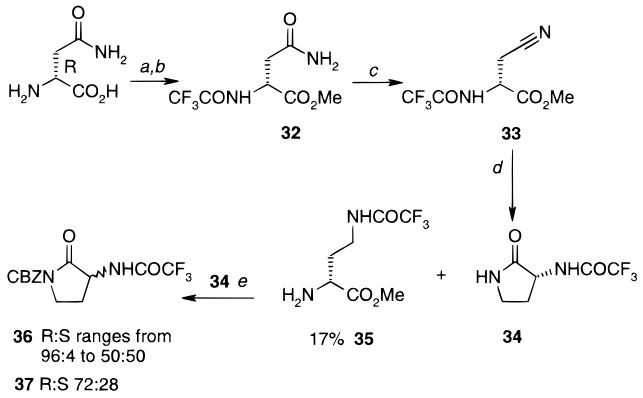
The most obvious option was to repeat the chemistry described previously (Scheme 3), starting from enantiomerically pure diaminobutyric acid **30**. We chose not to pursue this option, primarily due to the high cost of diaminobutyric acid[21] and also because the biological profiles of related compounds of known absolute stereochemistry led us to predict that analogues of the 6*S*,6a*S*,3a*R* *trans*-lactam **28** would be those having the greater biological activity. A retrosynthetic analysis indicated that (*R*)-diaminobutyric acid would be the required starting material, and this was not available commercially.

After a thorough search of the literature, we decided to investigate routes to enantiomerically pure *trans*-lactam **28** from either asparagine or methionine via the imide **31** (Scheme 6). Both enantiomers of asparagine and methionine are commercially available, with (*R*)-asparagine being cheaper than (*R*)-methionine.[22] We thus initially chose (*R*)-asparagine as our starting material.

An Approach to Enantiomerically Pure Isopropyl *trans*-Lactam 28 from (*R*)-Asparagine

(*R*)-Asparagine was converted into its trifluoroacetamide and then into the corresponding methyl ester **32** according to literature procedure[23,24] (Scheme 7). Dehydration of the primary amide using tosyl chloride and

Scheme 7[a]



[a] Key: (a) CF_3CO_2Me, Et_3N, MeOH, rt, 70%; (b) AcCl, MeOH, −70 to −20 °C, 57%; (c) TsCl, pyridine, CH_2Cl_2, rt, 59%; (d) Rh on Al_2O_3, H_2, EtOH, rt, 23−26%; (e) *n*-BuLi, THF, −70 °C; then CBZCl, rt, 55−70%.

pyridine gave, after chromatography, a 59% yield of the nitrile **33**.[25] Hydrogenation of the nitrile **33** with rhodium on alumina[26] followed by an intramolecular cyclization gave, after chromatography, a 26% yield of the cyclic lactam **34** with a major byproduct being the trifluoroacetamide **35** (17% yield). Reaction of the lactam **34** with 1 equiv of *n*-butyllithium at −70 °C followed by addition of benzyl chloroformate and warming to 0 °C or room temperature gave yields from six experiments of 55−81% of the desired imide **36**. However, analysis of the products **36** by chiral HPLC showed that the enantiomer ratios varied from *R*/*S* 50:50 to *R*/*S* 96:4. We did not investigate extensively the origins of this loss in optical purity, although clearly under certain conditions optical purity may be maintained.

A batch of imide **37** (*R*/*S* 72:28) was progressed as before (in 34% overall yield) to give the *trans*-lactams **28** (6*S*,6a*S*,3a*R*) and **29** (6*R*,6a*R*,3a*S*) in a ratio of 74:26, suggesting that optical integrity is maintained during this reaction sequence. Comparison of this synthetic material by analytical chiral HPLC with the enantiomers **28** and **29**, which had been separated by preparative chiral HPLC, allowed their absolute stereochemistry to be assigned:[27] the stereochemistry of our potential lead candidates was confirmed as 6*S*,6a*S*,3a*R* (as in **1**). Although this chemistry allowed us to assign absolute stereochemistry, the tendency toward racemization during the benzyl carbamate protection step and the low yields led us to investigate (*R*)-methionine as an alternative starting material.[28]

Large Scale Route to Enantiomerically Pure Isopropyl *trans*-Lactam 28 and Crotonamide 1 from (*R*)-Methionine

Construction of pyrrolidones from methionine is known from the work of Freidinger *et al.*,[29] and this method was

(20) The racemate **2** may be separated into its enantiomers by preparative HPLC on a 2 in. Merck AD column, eluting with 15% ethanol/heptane with a flow rate of 50 mL/min. The injection volume is 25 mL, and the detector wavelength is 215 nm. The throughput of material is limited by the solubility of **2** in the mobile phase (100 mg/25 mL). The 6*S*,6a*S*,3a*R* enantiomer **28** elutes first and can be obtained in satisfactory purity without recycling. The 6*R*,6a*R*,3a*S* enantiomer elutes second and requires one to two recycles to obtain material of satisfactory purity.

(21) (*R*,*S*)-2,4-Diaminobutyric acid dihydrochloride costs ca. £10/g. (*S*)-2,4-Diaminobutyric acid dihydrochloride costs ca. £20/g from Aldrich Chemical Co.

(22) (*R*)-Asn costs £25/100 g, (*S*)-Asn costs £14/100 g, (*R*)-Met costs £23/25 g, and (*S*)-Met costs £17/100 g from Aldrich Chemical Co.

(23) Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805−2807.

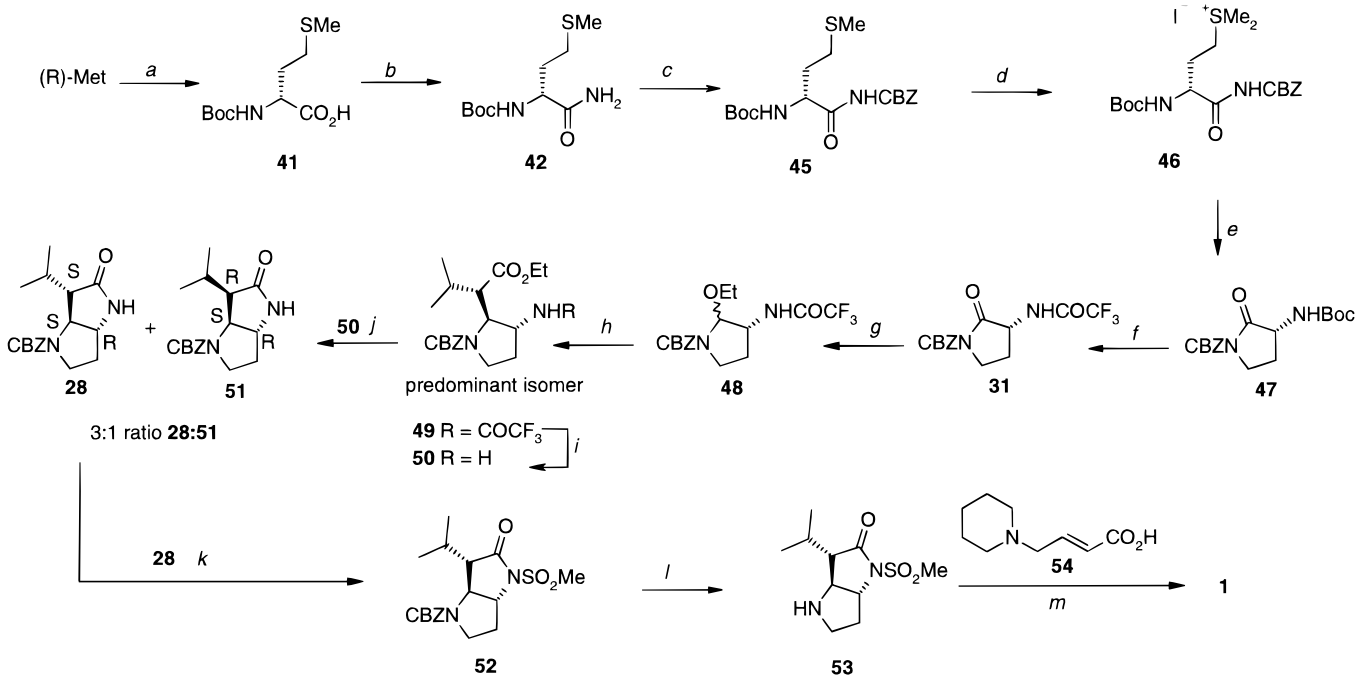
(24) Maddaluno, J.; Corruble, A.; Leroux, V.; Ple, G.; Duhamel, P. *Tetrahedron: Asymmetry* **1992**, 1239−1242.

(25) There is a tosyl-derived byproduct formed in this reaction, and its removal by chromatography also leads to degradation of some of the product.

(26) Galan, A.; de Mendoza, J.; Prados, P.; Rojo, R.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 452−454.

(27) Comparison of the circular dichroism spectra of the synthetic material (mainly **28**), the pure enantiomers **28** and **29** separated by chiral HPLC, and the C-6 allyl analogues of **28** and **29** (whose absolute stereochemistry had been determined by X-ray experiments) gave consistent results reconfirming the assignment of absolute stereochemistry.

Scheme 8[a]

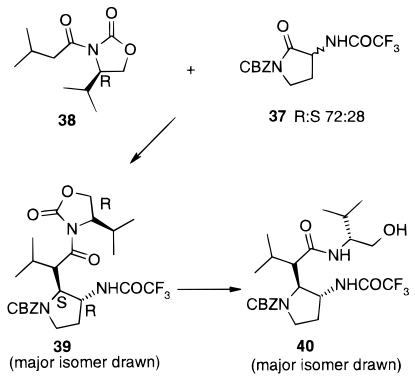


[a] Key: (a) Boc_2O, NaOH, H_2O, 1,4-dioxan, rt, 100% crude; (b) Boc_2O, pyridine, NH_4HCO_3, DMF, rt, 64−76%; (c) *n*-BuLi, THF, −70 °C then CBZCl, −70 °C, 100% crude; (d) MeI, Me_2CO or MeCN, rt, 77−88%; (e) Dowex 2X8−400 (hydroxide form), MeCN, rt, 67−76%; (f) 4 M HCl in 1,4-dioxan, rt then CF_3CO_2Me, $NaHCO_3$, MeOH or CF_3CO_2Me, *N*-methylmorpholine, CH_2Cl_2, MeOH, 85−93%; (g) $LiBH_4$, THF, −20 °C then cH_2SO_4, EtOH, rt, 90−99% crude; (h) *Z*-^{i}PrCHC(OSi^{i}Pr$_3$)OEt **24**, BF_3·OEt_2, CH_2Cl_2; (i) K_2CO_3, H_2O, EtOH, reflux; (j) *t*-BuMgCl, THF, TMEDA, rt, 17−36% for three steps; (k) $LiN(SiMe_3)_2$, THF, −70 to 0 °C then recool to −70 °C, $MeSO_2Cl$, 70−71%; (l) H_2, $Pd(OH)_2$, EtOAc, 1,4-dioxan, rt, 96−100%; (m) **54**, $Me_2NCH_2CH_2N{=}C{=}NEt$·HCl, 1-hydroxybenzotriazole, Et_3N, MeCN, rt, 64%; after purification 1 M HCl, Et_2O, CH_2Cl_2, rt, 87%. Alternatively **54**, $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt then **53**, $NaHCO_3$, CH_2Cl_2, rt, 85%.

used as the basis for our preparation of enantiomerically pure pyrrolidone **47**. We wished ideally to introduce the trifluoroacetyl group at the first step. However, due to the known propensity[30] of peptidic trifluoroacetamides to cyclize to oxazolidinones and to racemize under basic conditions, we decided to initially generate the *tert*-butyl carbamate derivative of methionine and to replace this protecting group with a trifluoroacetamide later in the synthesis.

On a 1.7 M scale (250 g), (*R*)-methionine was protected as its *tert*-butyl carbamate **41** and converted into the primary amide **42** (Scheme 8).[31] The yield after trituration was 64−76% over two steps.[32] Conversion of the primary amide **42** into the benzyl carbamate **45** was achieved using 2 equiv of *n*-butyllithium (for complete reaction) at −75 °C followed by addition of benzyl chloroformate. The product **45** was obtained in quantitative yield with greater than 96:4 *R*/*S* chiral purity.[33,34] The crude material was then treated with excess methyl iodide in acetone or acetonitrile at room temperature to give the sulfonium iodide **46** as a crystalline precipitate.[35] Isolation gave a 77−88% yield of **46** over two steps.

(28) In this homochiral series, we also investigated briefly the reaction of the ethers **37** with boron enolates of **39** in an attempt to improve the selective introduction of the isopropyl group. There is precedent that boron enolates can control the stereochemical introduction of substituents in a manner similar to our case. (See, for example: Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675−4676. Shirai, F.; Chiba, T.; Nakai, T. *Chem. Express* **1992**, *7*, 141−144. Pilli, R.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187−3190). Thus, treatment of **37** (*R*/*S* 72:28) with the boron enolate derived from **38** gave predominantly one isomer presumed to be **39** in 17% yield. ^{19}F NMR of the crude mixture indicated an 83:14:3 mixture of isomers. Attempted deprotection of the trifluoroacetamide failed, and reaction of **39** with lithium ethoxide led to ring opening of the oxazolidinone to give **40** in 60% yield rather than its displacement.

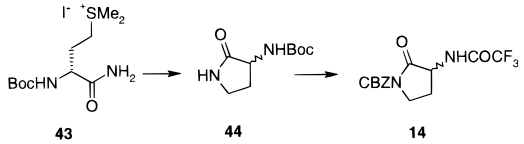


(29) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104−109.

(30) Bodansky, M. *Principles of Peptide Synthesis*; Springer-Verlag: Berlin, 1984; p 161.

(31) Pozdnev, V. F. *Tetrahedron Lett.* **1995**, *36*, 7115−7118.

(32) Initially, the *tert*-butyl carbamate amide **42** was treated with excess methyl iodide in ethyl acetate to give the sulfonium iodide **43**. Intramolecular cyclisation with sodium hydride gave the pyrrolidone **44** in 18% yield. After protecting the ring NH of **44** as its benzyl carbamate derivative (25% yield), deprotection of the *tert*-butyl carbamate and reprotection as the trifluoroacetamide (32% yield), analytical chiral HPLC showed the resultant pyrrolidone **14** to be racemic.



(33) An attempt to avoid the use of *n*-butyllithium by reaction of **42** with potassium carbonate, 18-crown-6, and benzyl chloroformate in a variety of solvents gave little or low yields of product **45**.

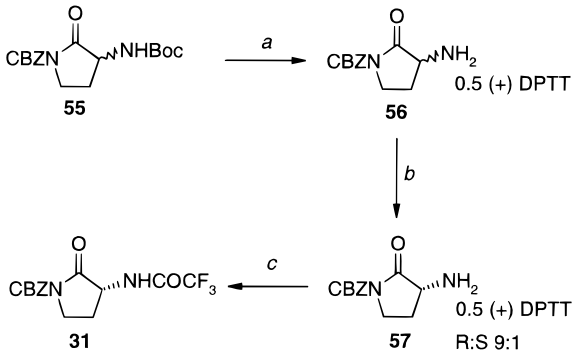
Cyclization of the sulfonium iodide **46** was achieved initially on a small scale using potassium hydride in THF and gave, after trituration with ether, a 42% yield of the pyrrolidone **47** of >98% optical purity. To avoid the use of potassium hydride on a large scale, we explored a variety of bases such as lithium hexamethyldisilazide, potassium carbonate, and hydroxide-exchanged Dowex 2X8-400 resin in a range of solvents such as acetonitrile, acetone, THF, and water. Potassium carbonate in acetonitrile gave good yields with little racemization in small-scale experiments, but on scale-up some racemization of **47** was observed. The preferred cyclization conditions were with *ca*. 1.3 wt equiv of Dowex resin in acetonitrile at room temperature. This routinely gave crude product **47** with *ca*. 9:1 *R*/*S*, which after one recrystallization from cyclohexane/ethyl acetate afforded optically pure product in 67−76% yields.[35]

Swapping the *tert*-butyl carbamate of **47** for a trifluoroacetamide was achieved as follows. Deprotection of **47** was effected with 4 M hydrogen chloride in dioxan over 4 h at room temperature. After removal of the dioxan, treatment of the residue with either sodium bicarbonate and trifluoromethyl acetate in methanol or *N*-methylmorpholine and trifluoromethyl acetate in dichloromethane/methanol gave, without further purification, 85−93% yields of >98% optically pure **31**.

The pyrrolidone **31** was converted into the *trans*-lactam **28** as shown in Scheme 8 using the conditions previously described. As expected, the chirality was preserved throughout. Analytical chiral HPLC of the crude *trans*-lactam product showed 3:1 **28**:**51** with less than 1% of the undesired *trans*-lactam enantiomer **29**. Recrystallization of the crude product **28** from ethyl acetate gave a 12:1 mixture of **28**:**51** with no other impurities. However, the preferred procedure was to purify the crude material by flash chromatography to remove all traces of **51**, since purification at the next stage was problematic.

The *trans*-lactam **28** was converted into the lead candidate **1** in a straightforward manner. Deprotonation of **28** with lithium hexamethyldisilazide followed by addition of methanesulfonyl chloride gave the acyl sulfonamide **52** in 70−71% yield after trituration of the crude product. The remaining 30% of the material was mostly unreacted starting material **28** that could be recycled. Removal of the benzyl carbamate with hydrogen over palladium hydroxide on carbon gave a 96−100% yield of the amine **53** as a crystalline white solid. Treatment of the piperidinocrotonic acid[36] **54** with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, hydroxybenzotriazole, and **53** gave a 64% yield of the free base of **1**. Alternatively, treatment of **54** with oxalyl chloride followed by the amine **53** avoided chromatographic purification and afforded **1** as the free base in the much higher yield of 85%. The salt was prepared with hydrogen chloride in ether/dichloromethane, and the hydrochloride was recrystallized from 2-propanol/ethanol to give material with less than 1% of any single impurity by analytical HPLC.

Scheme 9[a]



[a] Key: (a) TFA, CH_2Cl_2 then (+)-DPTT, rt, 96%; (b) cat. 3,5-dichloro-2-hydroxybenzaldehyde, THF, rt, 81%; (c) CF_3CO_2Me, *N*-methylmorpholine, CH_2Cl_2, MeOH, rt, 56%.

Using this synthesis, 9.5 g of the elastase inhibitor **1** was obtained from a 250 g input of (*R*)-methionine. This represents the yield obtained from a specific 14-step synthetic run and does not incorporate the best yields we have obtained for each step. It represents a 3.8 wt % yield and a 1.3% chemical yield. If the best conditions are used in each step, we estimate conservatively that a *ca*. 3% chemical yield could be obtained. The entire synthesis can be achieved in 25 working days (5 weeks) and requires glassware no larger than 10 L and only a single chromatographic purification. There are clearly refinements that can be made to further improve the efficiency of this process.

The Dynamic Resolution of a Key Intermediate

Having previously established the absolute stereochemistry of the desired *trans*-lactam **28** as that derived from an α-amino acid of unnatural chirality, the bulk availability of the amino acid as a starting material and its cost were evaluated. Other options, such as an alternative non-amino-acid starting material and introduction of the optical purity by an appropriate chiral reagent or resolution process were also considered. Of these, examination of a dynamic resolution of an intermediate used in the existing synthesis was very appealing because it would result in minimal deviation from the synthetic route in place and would also provide the opportunity to use an amino acid of natural chirality. These are readily available in bulk at lower cost.

On the basis of the precedent of induced dynamic resolution by crystallization,[37] the racemic pyrrolidone **55** was deprotected and treated with 0.5 equiv of (+)-di-*p*-toluoyltartaric acid (DPTT) to give the racemic salt **56** (Scheme 9). This material was dissolved in THF, and 4 mol % of 3,5-dichloro-2-hydroxybenzaldehyde was added. After the mixture was stirred for 6 days, a crystalline precipitate of **57** was obtained in 81% yield. Better yields

(34) Attempts to convert the acid **41** directly into the protected amide **45** via formation of the mixed anhydride and treatment with the lithium anion of benzyl carbamate failed.

(35) Numerous experiments to effect S-alkylation and intramolecular cyclisation in a "one-pot" reaction by treatment with methyl iodide, potassium carbonate, and a variety of polar solvents failed to give superior yields of the pyrrolidone **47** compared to the two-step procedure. Interestingly, warming **46** at 70 °C with or without K_2CO_3 in MeCN leads only to demethylation to give **45**. Warming **46** in toluene at 110 °C for 3 h gives 3:1 demethylation **45** to cyclization **47**. Further experiments to avoid methyl iodide by using trimethylsulfonium iodide (cf. Abood, N. A.; Flynn, D. L.; Laneman, S. A.; Nosal, R.; Schretzman, L. A. US patent 5,484,946, 1996) also failed to give acceptable yields of product.

(36) The piperidinocrotonic acid **54** was readily prepared in good yield by reacting ethyl 4-bromocrotonate with piperidine and potassium carbonate in acetonitrile followed by hydrochloric acid hydrolysis of the ester.

(37) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem*. **1987**, *52*, 955−957.

were obtained with THF as solvent than with methanol or acetonitrile. Treatment of the salt **57** with *N*-methylmorpholine and methyltrifluoroacetate in dichloromethane/methanol gave the trifluoroacetamide **31** as 9:1 *R*/*S* from chiral HPLC analysis. After one recrystallization, the trifluoracetamide **31** was obtained optically pure. Given that racemic methionine is dramatically cheaper ($18/500 g) than (*R*)-methionine ($49/25 g), this dynamic resolution process is highly attractive. Further developments incorporating this process on a large scale are currently being evaluated.

Conclusion

This paper summarizes the investigation of a number of routes to *trans*-lactams, leading to the discovery and development of a synthesis of enantiomerically pure *trans*-lactams that, with minor modification, can be executed on a multikilogram scale. The process can deliver high-purity compound **1** in bulk. Of particular interest is the stereocontrol in the acyliminium reaction, the crystallization-induced dynamic resolution, and a synthesis that only requires a single chromatographic purification.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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