Organic Process Research & Development **2008,** *12,* 322–338

Full Papers

Process Research and Development and Scale-up of a 4,4-Difluoro-3,3-dimethylproline Derivative

Francesco Rossi,[†] Francesco Corcella,[†] Francesco Saverio Caldarelli,[†] Franco Heidempergher,[†] Chiara Marchionni,[†] Miriam Auguadro,[†] Marco Cattaneo,[†] Lucio Ceriani,[†] Giuseppina Visentin,[†,‡] Giambattista Ventrella,[†,‡] Vittorio Pinciroli,[†,‡] Giuliano Ramella,[†] Ilaria Candiani,[†] Angelo Bedeschi,[†] Attilio Tomasi,*[,†] Billie J. Kline,[§] Carlos A. Martinez,[§] Daniel Yazbeck,[§] and David J. Kucera*[,§]

Active Pharmaceutical Ingredients and Analytical Development & Quality Control, Nerviano Medical Sciences, Pharmaceutical Sciences Unit Viale Pasteur 10, 20014 Nerviano, Italy, and Chemical Research and Development, La Jolla Laboratories, Pfizer Inc., 10578 Science Center Drive, San Diego, California 92121-1111, U.S.A.

Abstract:

The multikilogram production of the proline derivative 1, a key intermediate of a HIV protease inhibitor, required the design of a synthetic route able to be safely, effectively, and easily scaled up. Synthesis of the proline skeleton began with construction of racemic glycine derivative 4, via an ester enolate Claisen rearrangement of Boc-glycine 3-methyl-but-2-enyl ester (3) in the absence of a Lewis acid. After a classical resolution of 4 with (*S*)-phenylglycinol, (*S*)-4 was transformed into bromo-lactone 6b with NBS. The bromo-lactone was transformed to proline alcohol 8 via a base-promoted rearrangement involving lactone solvolysis. An NMR study suggested that a bicyclic lactone was initially formed, which subsequently opened by the methanol solvent to form 8. The requisite ketone for fluorination was prepared via oxidation of the enantiomerically pure 8, using NaClO and catalytic TEMPO. *gem*-Difluoro proline 1 was then prepared from the ketone via fluorination with Deoxo-Fluor. During this study it was discovered that SiO_2 promoted fluorination by Deoxo-Fluor. This study allowed the production of 7.5 kg of 1 after 10 steps, in 4.5% molar yield and high purity (94–99% HPLC assay).

Introduction

Proline derivative **1** is an intermediate for the synthesis of a HIV protease inhibitor.[1,2] Compound **1** Was originally synthesized by transformation of Boc-glycine **2** to iodo-lactone **6a**, which under basic conditions underwent a rearrangement to alcohol **8**, which was then oxidized to ketone **9**. *gem*-Difluoro derivative **10** was prepared by nucleophilic fluorination of **9**, and the title compound **1** was obtained enantiomerically pure by enzymatic hydrolysis of the ester group of **9**, using CLEC (cross-linked enzymes chrystals) subtilisin Carlsberg.

During scale-up of the original synthetic pathway, many liabilities were noted: (1) in the absence of an enantiomer recycling method, the bulk of the synthesis required twice the quantity of materials to be processed, (2) the CLEC subtilisin Carlsberg enzyme used in the optical resolution was no longer commercially available, (3) the overall yield of isolated **1** was about 1.5%, (4) the calculated sum of all materials (including solvents and reagents) needed to produce 2 kg of **1** was estimated to be about 13 t, (5) a large quantity of flammable solvents were employed (about 8,000 L for 2 kg of **1**), and (6) very low space−time yields were calculated (estimated frame time to produce 2 kg of **1** was of about 1 year). In order to furnish enough material, greater than 2 kg of **1** was required along with a more suitable synthetic pathway. New route exploration demonstrated the possibility to optically resolve intermediate **4** and use a single enantiomer throughout the synthesis. In this explorative study some racemization was observed during the basic rearrangement and the oxidation steps (**6** to **7**, **8** to **9**), affording the final product **1** with 62% ee from **4** with 96% ee. Thus, in light of these results and the liability of the original route, this new route was developed. The ensuing process development employed the following strategy: (1) quickly transform several hundred grams of material according to the unoptimized conditions to test the proposed procedure, which would allow establishment of analytical controls and provide material for examination of various steps, (2) identify potential issues for the scale-up in the available plant, (3) verify changes that may improve or simplify the process, (4) isolate and characterize all intermediates and their main by-product, (5) carry out the Process Safety Reviews (PSRs), (6) where necessary carry out a preliminary run at reduced scale, and (7) implement the process at full scale.

Results and Discussion

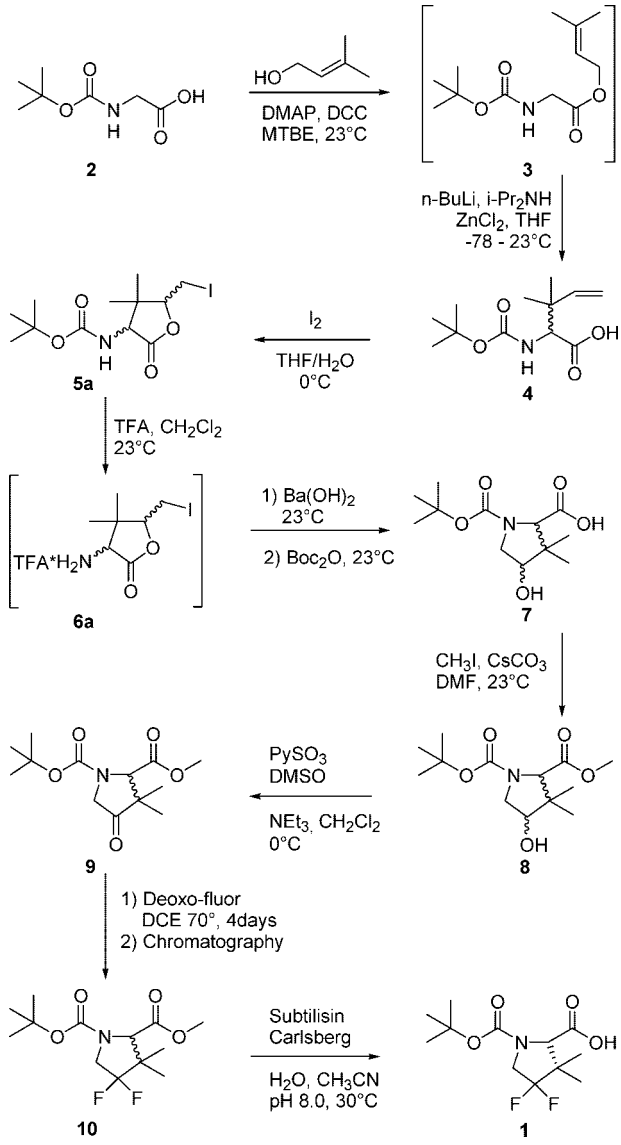
Esterification of Boc-Glycine. In the process originally developed, a solution of Boc-Gly-OH (**2**), 3-methyl-2-buten-1-ol (prenol), and *N*,*N*-dimethylaminopyridine (DMAP) in MTBE was treated with a solution of DCC. The resulting suspension was stirred at room temperature until disappearance of **2** was evident by HPLC. The suspension was then filtered,

* To whom correspondence should be addressed. Tel: +39.0331.58.1312. Fax: +39.0331.58.1348. E-mail: attilio.tomasi@nervianoms.com.
[†] Active Pharmaceutical Ingredients, Nerviano Medical Sciences.
[‡] Analytical Development & Quality Control, Nerviano Medical Sciences.
[§] Pfizer Inc.

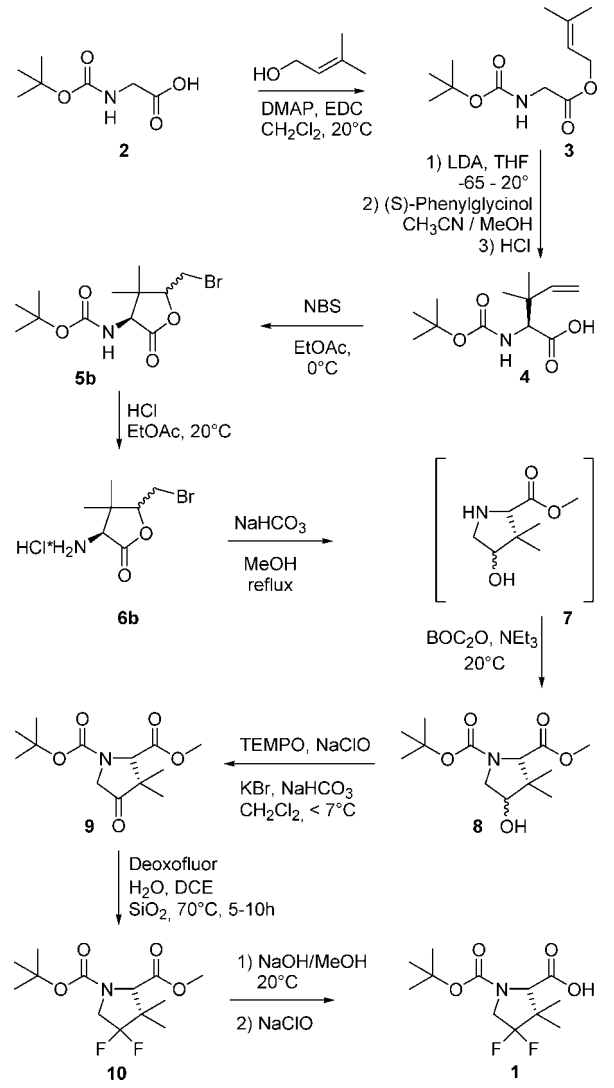
(1) Hammond, J. L.; Patick, A. K. U.S. Pat. Appl. Publ. 2005171038, 2005.
(2) Kucera, D. J.; Saeed, N. L.; Scott, R. W. PCT Int. Appl. 2005054187, 2005.

10.1021/op7001112 CCC: $40.75
Published on Web 02/21/2008

Scheme 1. **Original synthetic approach to 1; (*S*)-1 secured by enzymatic resolution of *rac*-10**



Scheme 2. **New route after development; (*S*)-4 obtained by a classical crystallization, thereby halving the total amount of material processed from intermediate 4 to 1**



and after an extractive workup, **3** was isolated almost quantitatively as pale yellow oil.

Limiting factors that were identified in the original procedure were large quantities of MTBE used (low flash point) and the filtration and drying of large amounts of DCU by-product. The filtration represented a major constraint for scale-up, because of the filter capacity in our plant. Another drawback was the residual prenol (about 15 mol %) present in isolated **3**, which would entail the use of additional LDA in the next step.

Substitution of DCC with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) was examined, since EDC and its corresponding urea are water-soluble. CH_2Cl_2 was chosen as the solvent in order to permit the reaction to be carried out in a very concentrated manner (about 30 wt % Boc-Gly-OH) with a very short cycle time. These conditions resulted in only a small quantity of residual prenol in isolated ester **3** (about 1.8% by HPLC assay). The urea by-product remained in the aqueous phase after the extractive workup, thus avoiding the filtration step. The product was isolated simply by concentration to a fluid oil of high purity.

These improvements allowed scale-up of the process to 30 kg of **2** in a 250-L reactor. Average results on this scale were 82% yield, 93.3% HPLC purity, and 93.0% HPLC assay.

Ireland−Claisen Rearrangement. The Claisen rearrangement of ester **3** to the glycine **4** derivative implied the use of $ZnCl_2$ as a Lewis acid, as this transformation is well-precedented. The yield of the original method for the sigmatropic rearrangement was high (about 80%). Nevertheless, there were concerns about scaling up this process to convert 120 kg of **3** in a 170-L cryogenic reactor, because of (1) high cost of the commercial $ZnCl_2$/THF solution; (2) toxicity of $ZnCl_2$; besides its high toxicity in an aqueous environment, it is also considered a potential mutagen and carcinogen; (3) low throughput; the dilute $ZnCl_2$ solution is about 50% of the reaction volume; processing of 120 kg of **3** with the original conditions in our plant would require 12 batches, 3 days per batch, 36 working days, 108 man-days, and 8 working weeks; (4) waste production; about 100 L of waste $ZnCl_2$ solution is produced per batch; moreover, $ZnCl_2$ must be destroyed separately from other process waste streams, according to the Italian and European laws.

11 12

Figure 1. **Major impurities isolated during the synthesis of 4.**

In the original procedure, the reaction mixture was held for 1 h at −65 ± 5 °C after LDA addition and was then warmed to 25 °C and allowed to react for about 6 h. Interestingly, the reaction required that prescribed time at 25 °C to reach the completion. When the reaction was quenched directly after LDA addition, only a 52% yield of **4** was obtained. The maximum conversion was obtained after about 4–5 h at 25 °C.

A literature survey indicated that $ZnCl_2$ can be replaced by Lewis acids commonly used for the Claisen rearrangement, such as BCl_3, $MgCl_2$, $AlCl_3$, etc.[3] Ireland and co-workers [4,5] first and Bartlett and co-workers[6] later showed the ability of trimethylsilyl chloride to promote the Ireland−Claisen rearrangement in the absence of the Lewis acid. These conditions[6] and modifications thereof were unsuccessful for the rearrangement of **3**.

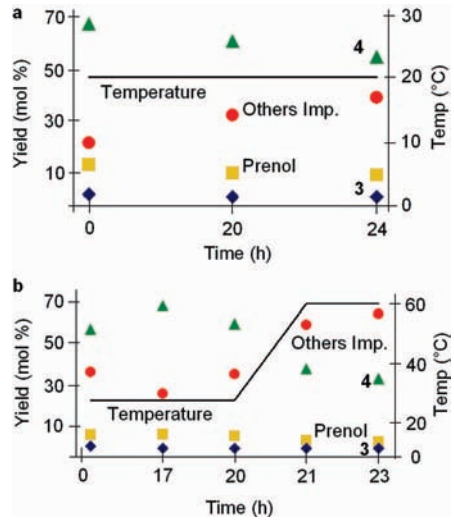
Although most Claisen rearrangements are performed in the absence of a catalyst, the Ireland−Claisen rearrangement seems to require either a Lewis acid or an enolate-quenching agent (such as trimethylsilyl chloride) to depress side reactions of the formed enolate. Kazmaier and co-workers[7] claimed that, in the absence of the stabilizing effect of a chelating metal (i.e., $ZnCl_2$), the corresponding lithium enolates of sterically demanding α-alkylated amino acids do not undergo the rearrangement but rather decompose during warming.

Despite these concerns, the aim was to develop a simple, safe, and productive process, and thus preparation of **4** in the absence of a Lewis acid was examined. Surprisingly, the yields of **4** produced in the first experiments were about 55%. Two major impurities were identified: urea **11** and carbamate **12** (although by-product **11** was isolated and characterized (see Experimental Section), the structure of **12** was inferred from its MS spectra $[C_{13}H_{20}NO_4]^-$ 254; $[C_8H_{10}NO_3]^-$ 168). The presence of **11** and **12** suggested that an excess of both LDA and prenol was detrimental to the quality and the yield of **4** and that optimization of the synthesis of **3** could play an important role by reduction of residual prenol and thus of LDA.

The new scenario outlined from these exploratory experiments was considered a promising starting point and an acceptable compromise between avoiding $ZnCl_2$ and obtaining slightly lower yields. Consequently this new approach was developed and optimized.

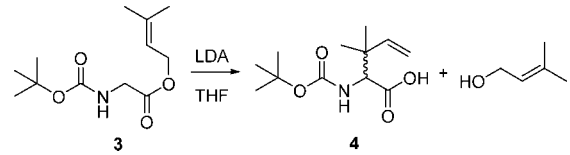
Once LDA was added to a solution of **3**, the mixture could be warmed to room temperature and then quenched. Conversely, after warming, the reaction mixture could be stirred for an additional period of time (maturation). A study aimed to establish the best operating procedure, including warming rate and maturation, period was undertaken. The results showed that

Chart 1. **Influence of maturation time and temperature during the Ireland−Claisen rearrangement of 3[a]**



[a] Product **4** slowly decomposed under isothermal conditions at 20 °C (graph a). Heating did not increase the extent of conversion, but rather decreased the quality and yield (graph b).

Table 1. **Effect of variables on the yield of 4 and the formation of prenol[a]**



3 4

entry	temp (°C)	LDA (equiv)	LDA addition (h)	**4** (mol %)	**3** (mol %)	prenol (mol %)
1	−30	2.2	0.5	54.6	1.8	17.8
2	−47.5	2.8	1.8	78.0	1.0	9.1
3	−30	3.4	3	51.2	2.5	19.6
4	−47.5	2.8	1.8	73.1	0.9	10.6
5	−65	3.4	0.5	81.6	0.8	7.7
6	−47.5	2.8	1.8	76.0	0.9	8.6
7	−65	2.2	3	78.6	0.9	9.2

[a] Temperature during LDA addition was an important variable. The yield and quantity of **4** decreased above −30 °C.

an increased maturation period (beyond 6 h) was detrimental to the yield and quality of **4**; a maturation period of 24 h reduced the yield of **4** from 70% to about 50%. Similar results were obtained for an increase in the maturation temperature; heating the reaction mixture from 20 to 60 °C dramatically increased impurities and decreased yields to about 30%. Additional studies indicated that the quality and yield of **4** were not dependent on the warming rate from −65 to 20 °C.

To better define the process, other variables were also examined: (1) reaction temperature (−65 to −30 °C), (2) LDA addition rate (0.5 to 3 h), and (3) LDA quantity (2.2 to 3.4 equiv). A set of experiments was designed using a fractional factorial design, three center points, and no replication. The data were fitted by linear regression analysis, and the regression explains 83% of the data ($R^2 = 82.7$).

From these experiments, only the reaction temperature appeared to be a critical variable. Maximum yields of **4** were

(3) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–247.
(4) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.
(5) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.
(6) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933–3941.
(7) Kazmaier, U.; Maier, S. *Tetrahedron* **1996**, *52*, 941–954.

Table 2. **Physical parameters of the salts between *rac*-4 and (*S*)-phenylethylamine and (*S*)-phenylglycinol determined by DSC[a]**

entry	salt	ΔH_p(kJ/mol)	T_{50} (K)	T_{eu} (K)	1/*C*	x_{eu}	R_{max} (%)
1	(*S*)-phenylethylamine/*rac*-**4**	5.9	424	409	18	0.37	20.3
2	(*S*)-phenylglycinol/*rac*-**4**	16.2	435	410	3.6	0.23	35.3

[a] ΔH_p is the melting enthalpy of the salt between (*S*)-**4** and the (*S*)-enatiomer of the chiral base. T_{50} is the melting temperature of the salt between *rac*-**4** and the resolving base. T_{eu} is the temperature at the eutectic composition. X_{eu} is the eutectic composition, and R_{max} is the maximum obtainable yield. *C* is given by the following formula:

$$C = \frac{1 - 2x_{eu}}{2 - 2x_{eu}} \ln 2x_{eu} = \frac{\Delta H_p}{R}\left(\frac{1}{T_{50}} - \frac{1}{T_{eu}}\right)$$

obtained at −65 °C (78–80%), but only a small decrease in yield was observed at −48 °C (about 75%). LDA addition at temperatures above −48 °C rapidly decreased yields, and at −30 °C yields were around 50% (Table 2, entries 1 and 3). The quantity of prenol formed during the reaction was temperature-dependent; it increased from 8−10% below −50 °C to 18–20% at −30 °C. No correlation was detected for residual starting material **3**, which was constant at 1.0–2.5%.

The reaction was further investigated, using in situ ATR FTIR analysis, with the aim to understand better the role of temperature and the stability of the species formed during the rearrangement. The reaction was run several times under the optimized conditions, and IR analysis evidenced two major changes occurring during the transformation from **3** to **4**: (1) the decrease of the absorption bands at 1752 and 1714 cm^{-1}, and (2) the formation of a new absorption band at 1620 cm^{-1}.

From the comparison of IR spectra of Boc-Gly-OH **2**, ester **3**, and acid **4**, the absorption bands at 1752 and 1714 cm^{-1} were assigned to the *C*═O stretching of the Boc group and of the ester and acid moiety present in **3** and **4**, respectively. The signal at 1620 cm^{-1} was assigned to the stretching of the aza-enolate and of the conjugated enolate formed upon addition of 1 and 2 equiv of LDA, respectively. This assumption was confirmed by reaction of the lithium salt of **2** with LDA; the addition of LDA caused the appearance of a signal at 1620 cm^{-1}, whose intensity doubled after addition of the first equivalent of LDA. Since this substrate cannot undergo sigmatropic rearrangement, this can be explained with the sequential formation of the aza- and conjugated enolates.

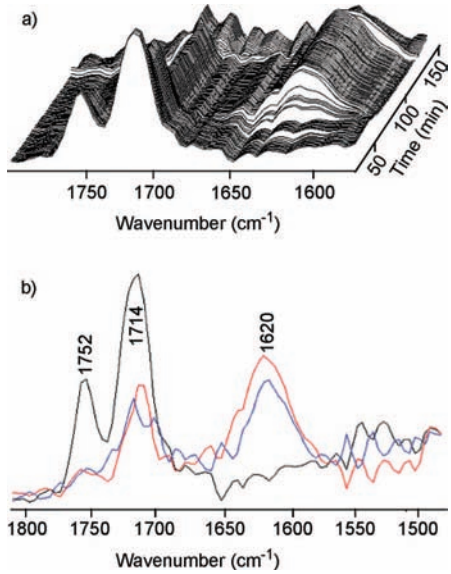


Figure 2. **(a) ART FTIR analysis of the rearrangement of 3. The addition of LDA caused formation of a new absorption band around 1620 cm^{-1}. The absorbance of this new signal was proportional to the quantity of added LDA. It remained constant after the end of addition and for an aging time of about 1 h. (b) Selected IR spectra before addition of LDA (black), after addition of 2 equiv of LDA (red), and after raising the temperature to 0 °C (blue).**

The collection of the IR spectra recorded during the reaction was analyzed by chemometric software. During LDA addition at −65 °C, the absorption band at 1620 cm^{-1} increased, while the absorptions of the starting material (1752 and 1714 cm^{-1}) correspondingly decreased. The formation of the new species was fast[8] at cryogenic temperature; the transformation time was approximately 1 min, since IR spectra were collected every min. Nevertheless, once the intermediate was formed, it remained unchanged for at least 1 h at − 65 °C. As soon as the temperature was raised to 0 °C, this intermediate species suddenly rearranged.

These experimental results can be explained by the following: (a) Ester **3** reacts quickly with LDA at −65 °C, forming sequentially the aza- and the conjugated enolate **3a** and **3b**. (b) Enolate **3a** and **3b** is quite stable at cryogenic temperatures but becomes highly reactive when the temperature is warmed to 0 °C. (c) At around 0 °C, enolate **3b** undergoes rearrangement, eventually forming **4a**. Parallel to this mechanism, another pathway can occur, leading to the formation of by-product. For example, either the aza-enolate **3a**, conjugated enolate **3b**, or product **4a** can decompose to isocyanate species **3c**, **3d** and **4b**, respectively, which in turn can react with prenol or LDA to yield impurities **11** and **12**.

From this investigation, the cryogenic temperature appears necessary to prevent decomposition of aza-enolate **3a** to isocyanate **3c**. Once the conjugated enolate **3b** is formed, it is reasonably stable and must be warmed to effect the sigmatropic rearrangement. When Boc-Gly-OLi was reacted with only 1 equiv of LDA at −65 °C, followed by warming to 0 °C, in situ ATR FTIR spectroscopy revealed disappearance of the Boc signals. The resulting mixture was then quenched with EtOH, to yield the ethyl carbamate of glycine.

In the original process, **4** was isolated as an oil after phase separations and concentration using MTBE as main solvent.

(8) Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. *Chem.−Eur. J.* **2001**, *7*, 4117–4125.

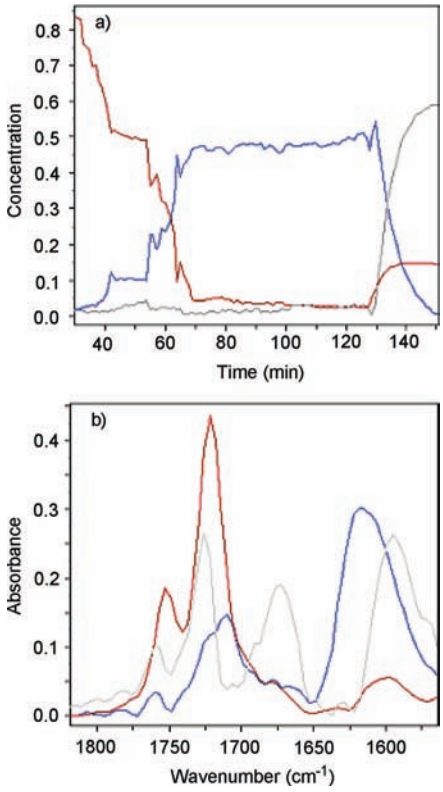
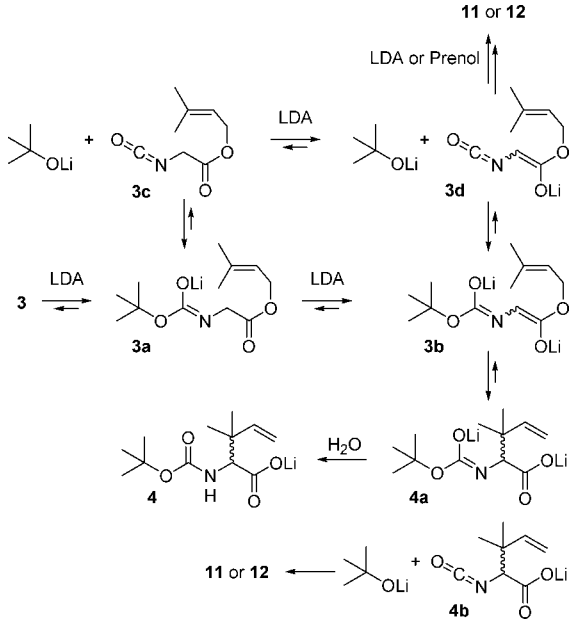


Figure 3. **(a) Concentration profiles of the main species present during the reaction. The first intermediate (blue profile) formed upon addition of LDA, while the concentration of starting 3 decreased (red profile). When the temperature was raised to 0 °C (around 130 min) the conjugated enolate disappeared, eventually forming the product 4a (gray profile). (b) The calculated IR spectra relative to the main reaction species are in good agreement with the expected spectra. The red profile corresponds to 3, and the blue profile corresponds to 3b. The gray curve has characteristic signals at about 1754 and 1712 cm^{-1}, as expected for 4 or 4a.**

Scheme 3. **Rationalization of the [3,3]-sigmatropic rearrangement of Boc-glycine ester 3**



To simplify the workup, isolation of **4** directly from water at acidic pH in the absence of MTBE was envisioned. A procedure was developed in which the reaction mixture was quenched into water, and the rich organic phase was then extracted with aqueous NaOH. Some hexane was added to the rich aqueous layer, and the pH was then adjusted to 2–3 with aqueous HCl, which afforded **4** as a filterable solid. Hexane was found useful for removal of lipophilic impurities, which otherwise caused oiling out of product **4**. The isolation of intermediate **4** as a solid improved the quality. Obtaining this racemic mixture with a consistently high purity was a prerequisite for ensuring a successful optical resolution.

The optimized process was employed for the campaign production of **4** from 117 kg of **3**, using the following conditions: 2.5 equiv of LDA at −65 °C, with a 2–3 h LDA addition time. Residual **3** was about 0.8%, formed prenol was about 8.0 mol %, and the yield of **4** was about 84.7% before quenching (HPLC assay) and 72% isolated. Interestingly, after optimization, the performance of the $ZnCl_2$-free process was comparable to that of the original process that included $ZnCl_2$.

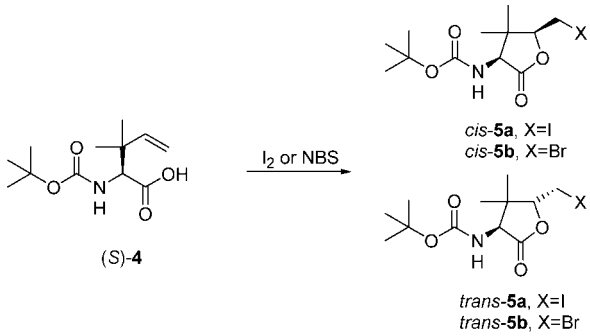
Optical Resolution. Early studies indicated that enantiomerically pure phenylglycinol or phenylethylamine were suitable optical resolution agents for **4**. To accelerate the choice between these two chiral bases, the DSC-based approach developed by Kozma and Bruggink [9,10] was implemented. According to this method, DSC analysis of the salt formed by racemic **4** and the resolving agent gives the eutectic composition (x_{eu}), which indicates the maximum obtainable yield[11] and therefore the effectiveness of the studied resolving agent. [The maximum obtainable yield is always lower than 50%, according to the equation $R_{max} = 100 \cdot (0.5 - x_{eu})/(1 - x_{eu})$]. DSC analysis of racemic **4** and phenylethylamine gave a maximum obtainable yield of 20%, while the value calculated for the phenylglycinol system was greater (35%). On the basis of these results, phenylglycinol was chosen as a resolving agent.

Using enantiomerically enriched **4**, the entire cascade from intermediate **4** to final product **1** was run to confirm that (+)-(*S*)-phenylglycinol was the enantiomer to be used to isolate desired (*S*)-**4** and eventually **1**.

Early solvent screening indicated that the resolution performed well with a mixture of CH_3CN/MeOH. With the aim to find a less toxic and less flammable solvent system, other solvents were explored. Among other solvents, attention was focused on acetone or CH_3CN and H_2O. Acetone/H_2O (9:1) dissolved salt n 5-fold more than salt p (the desired diastereomeric salt) and afforded salt p in 100% ee, but unfortunately in low yields (28%). [According to the nomenclature proposed by Wilen and co-workers,[11] salt p refers to the salt pair for which the sign of the optical rotation for each component of the salt is the same (for instance (+), (+) or (−), (−)]. Conversely, salt n was approximately 10-fold more soluble than salt p in CH_3CN/MeOH (9:1), which in principle should lead to high purity and higher yields. It was found that salt p can be resolved up to 86% ee after one crystallization and that the quality can be improved up to the target 96% ee by suspension of the salt

(9) Kozma, D.; Pokol, G.; Acs, M. *J Chem. Soc., Perkin Trans. 2* **1992**, 435–439.
(10) Ebbers, E.; Ariaans, G. J. A.; Zwanenburg, B.; Bruggink, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2745–2753.
(11) Jacques, J.; Collet, A.; Wilen, S. H. Enantiomers, Racemates, and Resolutions; Krieger Publishing Company: Malabar, FL, 1994.

Scheme 4. ***cis*-Lactone isomer favored from halolactonization (9:1)**



in the same solvent mixture (15 L of solvent for 1 kg of salt p). The whole process, from *rac*-**4** to purified salt p, was executed on a plant scale with 10 kg of *rac*-**4** and resulted in salt p with ≥96% ee and 42% yield (this value corresponds to a 40% yield (based on (2*S*)-**4**, 100% ee), which agreed well with the DSC-based yield estimation of 35%). It was observed that the composition of the mother liquors of the second treatment have the same composition as the material isolated from the first crystallization. Therefore by recrystallization from the CH_3CN/MeOH (9:1) mixture, an additional quantity of purified salt p was obtained. The overall yield in terms of purified salt p was 44%.

Racemization of the undesired enantiomer (*R*)-**4** was also examined. While no success was obtained in the direct base-mediated racemization of (*R*)-**4**, the corresponding methyl ester was racemized after refluxing in CH_3ONa/CH_3OH for 8 h. After ester saponification with NaOH, the resolution with (*S*)-phenyl glycinol provided the salt p in overall yields of about 30% (from recycled salt n to obtained salt p) and 96% ee.

Bromolactonization and Boc-Deprotection. The transformation of acid (*S*)-**4** to proline **8** was accomplished by cyclization to reactive halo lactone **5**, followed by rearrangement to proline **8**. During these transformations a new stereocenter is created but is of no consequence since it is destroyed after oxidation to ketone **9**. In the preliminary process studies, these transformations had been previously performed with *rac*-**4**, and thus preservation of the chirality from (*S*)-**4** to **1** had to be proven. In the first evaluation it was discovered that the stereocenter α to the carboxyl was substantially preserved; partial racemization was observed during the basic rearrangement and oxidation step with $Py.SO_3$ (the ee decreased about 12% over these two steps). As far as the bromo-lactonization of **4** and the Boc-deprotection of **5** were concerned, no racemization was observed. During the cyclization of **4**, *cis* and *trans* diasteroisomers were obtained, and therefore substrates with potentially different reactivities were generated for the basic rearrangement to **8**. It was indeed found that the *cis* isomer reacted more quickly and more cleanly than the *trans* isomer (vide infra), and fortunately, lactonization was selective for *cis*-**5** (*cis*/*trans* ratio about 9:1).

Halo-lactonization could be effected with I_2 to give *cis*/*trans*-**5a** or with NBS to give *cis*/*trans*-**5b**. NBS was chosen as the preferential reagent because (1) only 1.1 equiv was needed, compared to 3 equiv of I_2 (greater atom economy); (2) consequently, less sulfite would be required for reduction of the unreacted reagent; and (3) NBS is cheaper than I_2.

EtOAc was chosen as reaction solvent because it could also be used for the recovery of (*S*)-**4** from salt p and for the Boc-deprotection of **5**. An additional advantage of EtOAc was that **6b** could be recovered quantitatively as its hydrochloride salt by performing the deprotection with HCl (g).

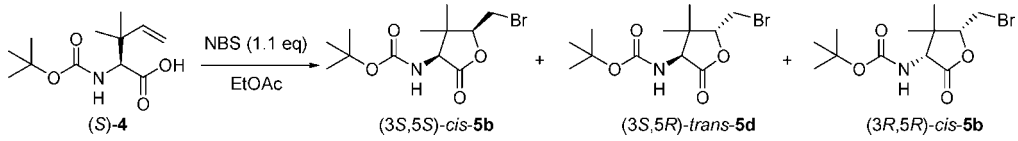
Examination of reaction variables for the preparation of **5b** focused on the reaction temperature and the influence of water (possibly carried in from the isolation of (*S*)-**4**). The presence of dissolved H_2O did not influence the yield or diastereomeric ratio (Table 3, entries 1 vs 2, and 3 vs 4,), but a lower temperature resulted in a slightly greater *cis*/*trans* ratio (Table 3, entries 1 and 3, or 2 and 4). The optimal conditions for the production of **5b** were set at 0 °C, with 1.1 equiv of NBS.

For removal of the Boc group of **5b**, the following conditions were explored: TFA/EtOAc, HCl(aq)/EtOAc, and HCl (g)/EtOAc. The goal was to obtain **6b** as a filterable solid directly after the deprotection, avoiding distillation or other manipulations. TFA was eliminated because of its cost and the formation of by-product. HCl(aq) was eliminated because a substantial amount of **6b** remained dissolved and thus low yields were obtained. HCl(g)/EtOAc proved to be the best solution. After some trials the optimal concentration of *cis*/*trans*-**5b** in EtOAc and the stoichiometry of HCl were defined (Table 4, entry 3). Complete deprotection of **5b** required about 14 h, but most of the conversion occurred in the first hour, which was followed by sudden crystallization of **6b**. To avoid the spontaneous crystallization, HCl was charged in two portions 1 h apart.

This process was implemented in the plant, and **6b** was obtained in 91% yield and 93:7 *cis*/*trans* ratio, with a somewhat long filtration and drying time (1 day).

Rearrangement to Proline Skeleton and Boc-Protection. The transformation of bromolactone **6b** to proline derivative **8** requires lactone methanolysis followed by displacement of the halogen atom by the amine group. During early development, various quantities of $NaHCO_3$ and K_2CO_3 were investigated under various conditions. The major issues were low conversion of **6b** to **8** and epimerization of the α-carbon (about 7%). [Since the two stereocenters of **6b** are not involved in the basic rearrangement, their configuration should be preserved. Nevertheless the acidity of the proton at the α-carbon might in principle lead to partial epimerization, with the consequent formation of diastereomers.] Two opposite results were obtained combining different reagents and different temperatures: K_2CO_3 (2–3 equiv) and methanol at reflux resulted in complete conversion but also epimerization, whereas $NaHCO_3$ (2–3 equiv) in methanol at 25 °C resulted in no epimerization but low conversion. One approach to obtain good conversion and low epimerization would be to decrease the strength of the base and increase the reaction temperature, or to reduce the stoichiometry of the base. Reduction of base from 2 to 1 equiv would hypothetically lead to a reaction mechanism in which the role of the base consists only of deprotonation of amonium salt **6b**. The free amine would in turn displace the bromine atom to form a bicyclic lactone, which would then be opened by methanolysis. Our hypothesis was supported by the isolation of bridged-amino lactone **13**, after Boc-protection of the reaction mixture.

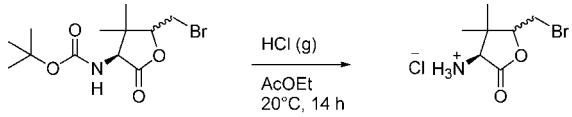
Table 3. **Optimization of the bromo-lactonization[a]**



entry	conditions	yield (%)	*cis*/*trans*(A% HPLC)	chiral HPLC (A%) (3*S*,5*S*)-*cis*-**5b**	(3 *S*,5*R*)-*trans*-**5d**	(3*R*,5*R*)-*cis*-**5b**	(3*R*,5*S*)-*trans*-**5d**
1	salt p[b]; −20 °C; no stripping	98	96:4	94.3	4.3	1.4	nd[c]
2	salt p[b]; −20 °C; stripping	98	96:4	94.4	3.9	1.7	nd
3	salt p[b] ; 30 °C; no stripping		91:9	89.0	8.7	1.9	nd
4	salt p[b] ; 30 °C; stripping	94	92:8	90.2	8.2	1.6	nd

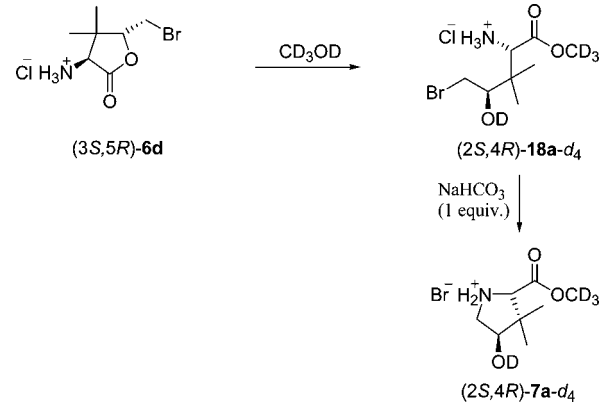
[a] No epimerization was observed in all cases. [b] Diastereomeric ratio = 97.8:2.2. [c] nd = not detected.

Table 4. **Optimization of the concentration and quantity of HCl**



entry	**5b** (M)	HCl(g) (equiv)	yield **5** (mol %)	yield **6** (mol %)	quality HPLC purity (A%)	quality **6** *cis*/*trans*
1	0.5	2	21	73	99.5	90:10
2	0.6	2	17	78	99.5	91:9
3	0.5	2 + 2		93.6	99.5	91:9
4	0.6	2 + 2		89.4	99.1	91:9

Scheme 5. **Reaction of *trans*-(3*S*,5*R*)-6d with 1 equiv of $NaHCO_3$**

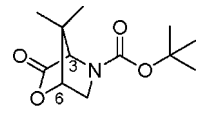


To verify the hypothesis, an experiment was performed with only 1 equiv of $NaHCO_3$ in refluxing methanol. Thus, pure enatiomer (3*R*,5*R*)-**6c** [because of the availability of pure intermediates in early studies, the undesired enantiomer was used for this evaluation] and 1 equiv of $NaHCO_3$ were mixed with deuterated methanol in a NMR tube, and reaction progress was followed by ^1H NMR. Graphically, the results of the first experiment showed a decreasing amount of **6c** and an increasing amount of transient intermediate **14** (as observed by Kazmaier and co-workers[12]), which reached a maximum after about 6 h of heating. [The bicycle is easily identified from the very small coupling constants of the two geminal hydrogens with the bridgehead hydrogen, which is about 1 Hz for the exoproton and nearly zero (not measurable) for the endoproton.]

The NMR data further showed complete disappearance of the *cis* isomer after 36 h, and no epimerization since only **7**-d_4 was formed. [It must be considered that the reaction rate observed in the NMR experiments could be less than the rate observed for a standard reaction as the result of an isotope effect, as deuterated methanol takes part in the reaction as a reagent, and also because of the fact that the heterogeneous mixture ($NaHCO_3$ in MeOH) was not stirred.] The concentration of cyclic intermediate **14** reached a maximum early in the reaction and evolved to product, which supported the proposed mechanism. After completion, the reaction mixture was treated with NEt_3 and Boc_2O. HPLC analysis then showed that epimerization had not occurred.

The same experiment was performed with (3*S*,5*R*)-**6d** (containing about 1% of diastereomer (3*R*,5*R*)-**6c**). In this experiment a certain degree of epimerization of the starting material was noted, as the detected amounts of (3*R*,5*R*)-**7**-d_4 and **14** were greater than expected. [The expected quantity of **14** was about 0.04%, which is 40% of the starting (3*R*,5*R*)-**6c** (1%).]

Since the conversion was still not complete after 36 h (an indication that the *trans* isomer reacted more slowly than the *cis*), the reaction was continued for a total of 52 h. At this point, NMR analysis showed almost complete disappearrance of all starting material and a mixture of two products in 73:27 ratio. The minor product was expected to be the diastereomer of **7a**-d_4, namely, **7**-d_4. In order to unambiguously identify the NMR signals of these two products, a sample of **8** with a *cis*/*trans* ratio of 87:13 was treated with HCl in EtOAc to give the corresponding diastereomeric mixture of **7** and **7a**. This allowed interpretation of the secondary product present after 52 h, which was confirmed to be (2*R*,4*R*)-**7**-d_4. The end-reaction mixture was then treated with Boc_2O, and HPLC analysis revealed a

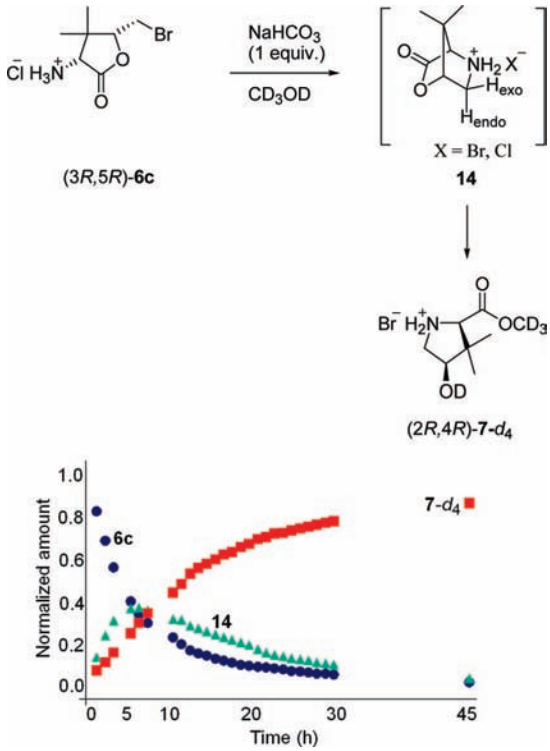


13

Figure 4. **Cyclic intermediate 13 isolated after Boc-protection of proline derivative (2*R*,4*R*)-7.**

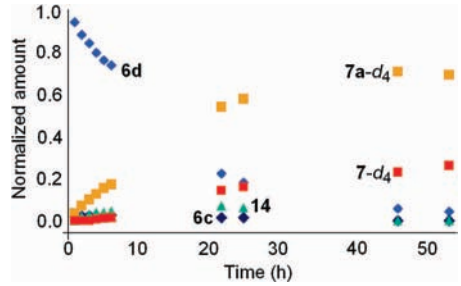
(12) Mues, H.; Kazmaier, U. *Synthesis* **2001**, 487–498.

Chart 2. **NMR study of the rearrangement of *cis*-6c[a]**



[a] Cyclic intermediate **14** was formed early in the reaction, and subsequently transformed into **7**-d_4.

Chart 3. **NMR study of the rearrangement of *trans*-6d**



cis/*trans* ratio of 26:74, confirming the epimerization observed by NMR analysis.

Before scaling-up the new conditions, alternate bases were briefly investigated. Epimerization was not observed with 1 equiv of NEt_3 or K_2CO_3, but some epimerization was observed when ≥1.5 equiv of base was employed. Consequently, the optimized process was defined as the use of no more than 1.2 equiv of $NaHCO_3$ and a reaction time of ≥17 h at 65 °C and ambient pressure.

During scale-up, an impurity was observed in Boc-protected proline **8**. On the basis of its molecular weight (LC-MS), it was inferred to be dimer **15**, formally resulting from the addition of **6b** to **8**. This impurity suggested that concentration may be a critical factor. We hypothesised that the bromine atom might be substituted by a nucleophile. We therefore envisaged a method to purge the impurity, provided that it would be transformed into a basic species, which can be then extracted by acidic water. Treatment of the **8**/**15** mixture with 1,2-ethylenediamine produced a mixture of **8** and **16**, from which **16** was selectively washed out with HCl(aq) to afford pure **8**

Scheme 6. **By-product 15 found during the synthesis of 8; 15 could be converted to amine 16 and then extracted by acidic water**

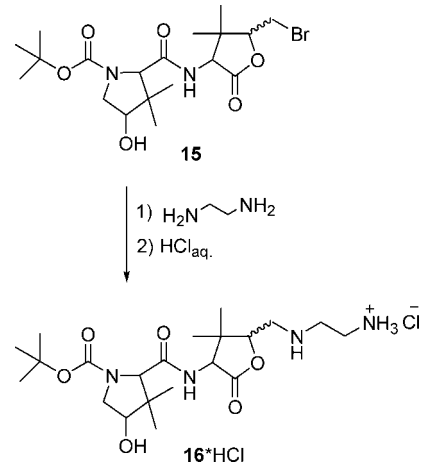
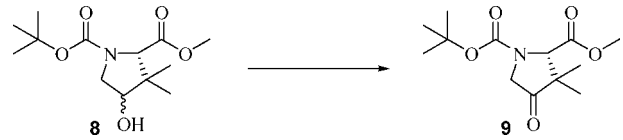


Table 5. **Exploration of alternate oxidation reagents[a]**



entry	oxidant	time (h)	conversion[b]	racemization (%)
1	Pyr·SO_3/DMSO[c]	3	complete	10
2	PCC	20	complete	40
3	NMO/TPAP	2	incomplete	33
4	NMO/$RuCl_2(PPh_3)_3$	2	incomplete	n.a.[d]
5	7% NaOCl/AcOH	20	incomplete	9
6	14% NaOCl/AcOH	20	complete	11

[a] The NaOCl/AcOH conditions produced as much racemization as the original Pyr·SO_3/DMSO conditions but reduced the hazard/pollution issues related and the costs. [b] Disappearance of (2*S*)-**8** (TLC). [c] Original conditions. [d] Coeluted with an uncharacterized impurity during HPLC analysis.

(LC-MS analysis performed on the aqueous phase after purification showed MW = 442, giving evidence of the proposed structure).

A comparison between the early and optimized processes showed that the yield from **4** to **8** was improved from 33% to about 73%, which allowed for the conversion of 35 kg of (2*S*)-**4** into 29 kg of **8**.

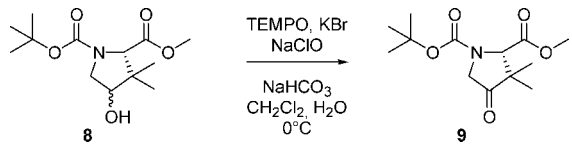
Oxidation. The initial procedure for oxidation of racemic alcohol **8** to ketone **9**, using Pyr·SO_3/DMSO, was performed successfully on the racemic series in reasonable yields (80% after chromatography). When (2*S*)-**8** was oxidized under these conditions, about 10% racemization at the α-carbon occurred. With these conditions, there were also concerns about waste streams (Me_2S) and cost of Pyr·SO_3.

Of the alternate oxidation conditions explored (Table 5), it was discovered that NaOCl/CH_3CO_2H resulted in a similar extent of racemization but satisfied the waste stream and cost issues. Milder conditions with NaOCl were permitted by inclusion of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).[13]

The NaOCl/TEMPO conditions were then optimized to minimize racemization, increase yields, and establish a safe and

(13) Lucio Anelli, P.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.

Table 6. **Optimization of the oxidation conditions**



entry	NaOCl (equiv)	TEMPO (mol %)	KBr (mol %)	$NaHCO_3$[a]	purity of **9** (A%)	assay of **9** (%)	yield of **9** (%)
1	2.8	10.4	13.7	8% aq in NaOCl	63.0	80.0	84.0
2	2.8	10.4		8% aq in NaOCl	incomplete conversion		
3	2.8		13.7	8% aq in NaOCl			
4	1.1	1.0	1.0	solid in NaOCl	96.9	93.9	90.0
5	1.1	1.0	1.0	*b*	96.2	88.6	85.0
6	1.1	1.0	3.3	solid in NaOCl	99.2	96.8	98.0
7	1.1	1.0	1.0	solid in CH_2Cl_2[c]	97.0	99.2	104.0

[a] Unless otherwise specified, the amount of $NaHCO_3$ was adjusted to maintain pH 8. [b] No reaction was observed until $NaHCO_3$ was added (after 24 h). [c] The quantity of $NaHCO_3$ was optimized to 0.7 mol % relative to NaOCl.

environmentally friendly process (Table 6). The influence of some variables, such as the concentration of NaOCl and the ratio of the reagents of the catalytic cycle described by Montanari and co-workers,[13] were screened. NaOCl can be used in almost equimolar ratio to **8** (Table 6, entry 4) regardless of its concentration (5% and 13% NaOCl solutions), while TEMPO and KBr can be dosed in catalytic amounts (1 mol %; Table 6, entry 4). $NaHCO_3$ was used to buffer the reaction mixture at pH 8; without the pH buffer control, oxidation was not observed and degradation of **8** resulted (24 h). The reaction began when $NaHCO_3$ was added, and high conversion was achieved after 24 h (Table 6, entry 5). Under the optimized conditions, $NaHCO_3$ was added to a CH_2Cl_2 solution of **8**, TEMPO, and KBr, which was then charged with a 5% NaOCl solution. The conversion was complete within 1 h, and after workup, a quantitative yield of **9** was obtained with complete retention of chirality. After the quench of residual NaOCl with a 5% $Na_2S_2O_5$ wash, the oily product could be used directly in the next step. The oxidation was scaled up to 12.9 kg of **8** in a 250-L reactor, which afforded **9** in an average yield of 95.5% and 100% ee.

Fluorination. *gem*-Difluoro derivative **10** could be obtained by nucleophilic fluorination of ketone **9**. In principle, a variety of fluorinating reagents, such as SF_4, DAST, Deoxo-Fluor (DF), 2,2-difluoro-1.3-dimethylimidazolidine[14,15] (DFI), and *N*,*N*-diethyl-α,α-difluoro(*m*-methylbenzil)amine[16] (DFMBA), could effect this transformation. However, only DAST and DF could be used in our plant because of the toxicity of SF_4 and the dehydrating characteristics of DFMBA and DFI,[17] which would potentially increase the quantity of by-product such as fluoro-vinyl derivative **17**. Recently Hu and co-workers[18] have demonstrated the possibility to fluorinate the ketone **9** changing the Boc-protective group with the benzyl group, and substituting DF with SF_4, obtaining benzyl-protected **10** in higer hields.

DAST and DF possess similar reactivity towards ketones, but DF is more thermally stable than DAST,[19,20] and this was particularly relevant since the reaction required high temperature. To determine the maximum reaction temperature that could be safely used, a preliminary hazard study was performed. To determine whether the thermal history of a sample of DF could influence its stability or not, samples of DF in toluene were aged for 8 h at different temperatures (DSC analyses, from 40 to 90 °C), and then the samples were heated to 300 at 10 °C/min. In all experiments degradation began around 120 °C, but the energy released by degradation slightly decreased as the aging temperature increased. The decomposition that occurred during the aging at 80 and 90 °C was approximately 7% and 16% less than the expected, which indicated partial degradation during the isothermal aging. Further experiments with a Calvet calorimeter (C80) showed the onset of the decomposition to be around 70 °C, a value much lower than that detected by DSC (120 °C). Nevertheless the decomposition at 70 °C was negligible and became significant only around 100 °C (5 bar). This study indicated that, for safety reasons, the maximum reaction temperature should not exceed 70–80 °C.

In the first attempt to scale up the fluorination process, DF in 1,2-dichloroethane (DCE) was used in a glass reactor at 55 °C and gave **10** in 46% yield after chromatography. Although this process was acceptable at this stage, several major issues surfaced: (1) long reaction time (4 days), (2) requisite large quantity of DF (4.4 equiv), (3) use of toxic DCE, (4) low space−time yields, (5) extensive formation of by-product (especially **17** and **19**), and (6) requirement of chromatographic purification, poorly effective for removal of fluoro-vinyl impurity **17**.

The immediate goal with these fluorination conditions was to reduce the quantity of DF and to increase the reaction rate (the use of catalysts such as $BF_3 \cdot Et_2O$, EtOH, and CF_3COOH did not improve the conversion). It was subsequently found that the reaction rate could be increased by an increase in reaction temperature (70 °C), while the quantity of DF could be

(14) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618–1619.
(15) Sonoda, H. *Fain Kemikaru* **2002**, *31*, 5–12.
(16) Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S. *Tetrahedron* **2004**, *60*, 6923–6930.
(17) Umetani, H.; Sonoda, H.; Komatsu, H. *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 667–669.
(18) Hu, S.; Martinez, C. A.; Kline, B.; Yazbeck, D.; Tao, J.; Kucera, D. J. *Org Process Res. Dev.* **2006**, *10*, 650–654.
(19) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054.
(20) Messina, P. A.; Mange, K. C.; Middleton, W. J. *J. Fluorine Chem.* **1989**, *42*, 137–143.

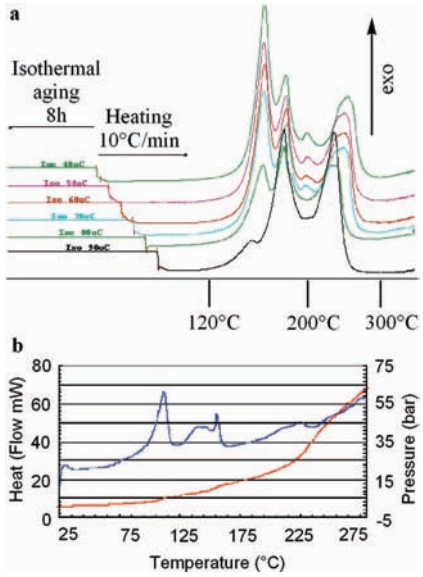
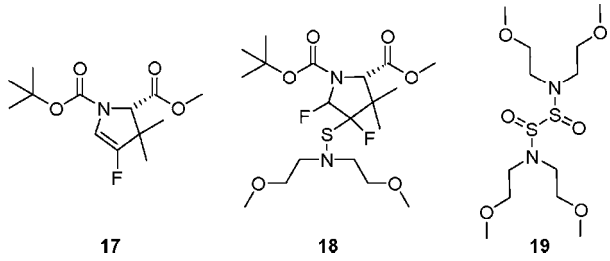


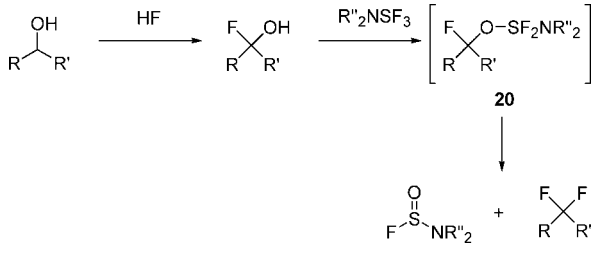
Figure 5. **Determination of the maximum safe fluorination temperature with DF. The DSC analyses established the decomposition onset at about 120 °C (black curve, graph a), while the C80 calorimeter detected the onset at about 75 °C (graph b). Nevertheless, the decomposition was modest and slow (blue curve, graph b), as shown by the slight pressure increase (red curve, graph b).**



17 **18** **19**

Figure 6. **The major by-products formed during the fluorination of 9 with DF. One characteristic of DF is the tendency to form compounds such as 19. These by-product are UV–visible and possess a molar extinction coefficient greater than that of 10 at 210 nm.**

Scheme 7. **Reaction mechanism proposed by Middleton**[22]



minimized to 1.3 equiv. With these optimized conditions, the reaction reached the maximum yield (40–45%) in only 8 h.

Although not supported by conclusive experimental proof, the following fluorination mechanism has been postulated: trace moisture reacts with DF to provide HF, which then adds to the carbonyl bond to form a fluorohydrin. This reacts with DF, generating HF and **20**. Further reaction of **20** with DF generates **10**, while creating additional HF catalyst.[21–24]

As DF reacts with the ketone **9**, two diastereomeric monofluoroderivatives (i.e., **20**) are formed. Different reaction pathways from each diastereomeric intermediate are possible as a result of steric and electronic effects, such as β-elimination to fluoro-vinyl **17**. Differential reactivities of the stereoisomers of **20** explain that the maximum observed yield of **10** observed was about 45%, with about 40% of unreacted **9** and about 10–12% of **17**.

To improve the selectivity of the fluorination and to simplify the purification, the effects of solvents, additives, and catalysts were screened. One goal was to explore whether the polarity of the medium could stabilize intermediate **20**[22] and prevent formation of **17** via β-elimination. Also, the presence of catalysts or additives could conceivably promote formation of **20** or convert by-product **17** via addition of a fluorine atom, both of which would lead to higher yields of **10**.[25,26] The first series of experiments employed H_2O, $NaHCO_3$, spray-dried KF (KF_{sd}), amorphous KF ($KF_{98\%}$), and Aliquat 336 (PTC) as catalyst and additives. [Other reagents used in the full factorial experimental design were $AlCl_3$, 18-crown-6, and TBAF. These reagents led to partial or complete degradation of ketone **9**. KF can be found commercially spray-dried form (KF_{sd}) or as an amorphous form ($KF_{98\%}$). In principle these forms could display different reactivities, because of their different solubility and adsorption properties. Nevertheless, KF_{sd} is more expensive and less available than $KF_{98\%}$. Aliquat 336 (trioctylmethylammonium chloride), a phase transfer catalyst, and 18-crown-6 were envisioned to promote addition of F^- to intermediate **20**.] For this evaluation, the following variables and ranges were selected: DF from 1.6 to 3 mol/mol of **9**; DCE from 0 to 0.68 mL/mmol of **9**; H_2O from 0.1 to 0.3 equiv; KF_{sd} from 1 to 2 equiv, and $KF_{98\%}$ from 1 to 2 equiv. [The quantity of DF exceeds the minimum quantity actually needed to convert the ketone **9** (1.3 mol/mol of **9**, as elsewhere stated in this article). The rationale is to supply that part of DF destroyed by the addition of catalysts and additives, which can be reactive or contain appreciable quantity of water.] To prevent extensive degradation of **9** and **10** when KF is used, $NaHCO_3$ must be included to reduce the acidity of the reaction medium. The screening set of 18 experiments (fractional factorial design resolution 5, 2 central points, no replications) was performed with an automated multiple reactor and the model validity was ascertained by statistical analysis of the results (ANOVA, R2, Q2, etc.).

The fitted model indicated that H_2O could range from 10% to 30% without any influence on the yield of **10**. Likewise, the quantity and quality of KF and the quantity of DCE had no influence on the results. The negative effect of decreasing DF is understood by considering that when water and/or KF are set at their upper value and DF at its lower one, most of the DF reacts with water and/or additives instead of with **9**, resulting in low conversions to **10**.

(21) Singh, R. P.; Shreeve, J. *Synthesis* **2002**, 2561–2578.
(22) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.
(23) Milos, H. In *Organic Reactions*; Milos, H., Ed.; Wiley: New York, 1988; Vol. 35, pp 513–637..
(24) Yin, J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. A. *Org. Lett.* **2004**, *6*, 1465–1468.
(25) Feiring, A. E. *J. Org. Chem.* **1980**, *45*, 1958–1961.
(26) Mase, T.; Houpis, I. N.; Akao, A.; Dorziotis, I.; Emerson, K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Molina, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775–6786.

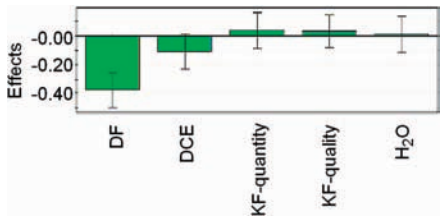


Figure 7. **Effect of variables in the fluorination of 9. The effect is negligible when the value is around zero or when the error bar crosses the zero line. In this case only the quantity of DF had an influence on the system.**

Analysis of the experimental data (Table 7) shows that the KF treatment did not react with **10** and only slightly decomposed **9** but was successful in the decomposition of **17** when DF was at its upper level of 3 equiv (Table 7, entries 2, 4, 8, 10, 12, 14). This finding was unexpected; the aim was to transform **17** into **10** or avoid its formation. Regardless, an effective method for elimination of **17** was discovered, and the goal to simplify the chromatographic purification of **10** was achieved.

The best conditions found were DF 3 mol/mol of **9**; H_2O 0.1 mol/mol of **9**, $NaHCO_3$ 0.2 equiv of **9**; $KF_{98\%}$ 1 equiv of **9** and PTC 0.1 mol/mol of **9**, 70 °C, 5 h for the fluorination, plus other 5 h for the decomposition. The results were (averange of 4 trials) the following: **10** about 40 mol %, the formed fluoro-vinyl **17** about 9 mol %, and the residual **9** about 37%. After decomposition with KF **9** and **10** remained unaffected (31 mol %, and 40 mol %, respectively), while **17** disappeared.

Accordingly to the best laboratory conditions, the process was scaled up in a 35-L Halar-coated reactor (Halar is a polifluorinated polymer resistant to HF). Unexpectedly, after 5 h of reaction, only 10% conversion to **10** had occurred. After an additional day of reaction and several doses of water, the conversion to **10** reached only 30%.

The root cause investigation revealed that the reactor material indeed influences the extent of fluorination. In particular, all of the experiments conducted in glass reactors were faster and performed better than those done in Halar or Teflon materials. This observation was contrary to the expectation that the inertness of Halar would allow for better performance because prevented reaction of DF with the reactor lining.

Since pitting of glass reactors occurred in the laboratory experiments, it was surmised that reaction of the silica glass with DF or generated HF produced a compound that had a positive effect on the fluorination. Reaction of a strong fluorinating reagent with silicates or SiO_2 would be expected to produce a fluorosilicate. Indeed, Padma and co-workers described the preparation of pyridinium hexafluorosilicate from SiO_2 and polypyridinium hydrofluoride (PPHF).[27,28] To confirm this hypothesis, the fluorination was tested in the presence of SiO_2 (1.5−10 wt % with respect to **9**) in a Teflon-lined multireactor system (a full factorial experimental design of 52 experiments was employed, using an Argonaut Quest 210 system, equipped with 20 10-mL Teflon reactors). It was found that small amounts of SiO_2 did promote the fluorination of **9**. Greater quantities of SiO_2 produced a negative effect, due to the fast reaction between DF and SiO_2, and resulted in decomposition of the DF. Also, in this case small quantity of water improved the reaction performance. Thus, 5 wt % SiO_2 (with respect to **9**) was included in the fluorination conditions.

This modified fluorination process was successfully implemented in a 35-L Halar-coated reactor and provided yields consistent with the laboratory trials (∼47% yield of **10**, 100% ee, and 0.1 mol % of residual **17** after the KF treatment). Crude **10** prepared in this manner could be purified by chromatography or, preferably, by chemical purification (vide infra).

Ester Hydrolysis. Partial racemization was observed in early studies of the basic hydrolysis of ester **10** with aqueous hydroxide and MeOH. Another issue observed was the low reaction rate (several days), presumably due to the lipophilic character of **10**. Development of this hydrolysis was aimed at establishing an acceptable balance between racemization and reaction rate, and two main variables were examined: the composition of the aqueous alkali solution and the quantity of methanol used as the cosolvent.

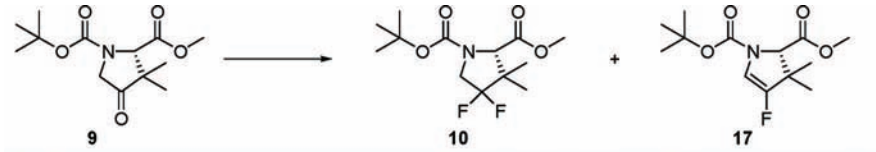
It was found that a high concentration of NaOH increased the reaction rate, but racemization was problematic (Table 8, entry 2 vs entry 1). Substitution of NaOH with LiOH, at the same concentration, depressed the reaction rate (Table 8, entry 3). The same negative effect was observed by a decrease in the quantity of NaOH (Table 8, entries 4 and 5). It was demonstrated that methanol was necessary for the reaction to proceed at a significant rate (Table 8, entry 6), although the volume could be reduced without affecting the reaction rate (Table 8, entries 7 and 8). The conditions in entry 5 (Table 8) were chosen for the production campaign, since a minimum quantity of base was used. Although the yield of these chosen conditions was lower than other conditions in Table 9, the yield increased up to 90% (from **10**) upon scale, due to easier manipulation of the solids on scale.

Purification of *gem*-Difluoro-ester 10 and *gem*-Difluoro-acid 1. The use of preparative MPLC (medium pressure liquid chromatography, stainless steel columns, 30 cm internal diameter, 1.5 m high, with a hydraulic-driven piston for compression of the silica gel (4 bar)) is demanding for production applications in terms of cycle time, use of solvents/silica, and waste generation Nevertheless, MPLC was used for the first scaled batches since extractions did not remove residual **9**, **18**, and the DF-related by-product.

During the saponification studies, a structure-dependent hydrolysis rate was observed; unreacted ketone **9** hydrolyzed much faster than **10** (a few hours for **9** vs 4 days for **10**). Moreover, it was discovered that NaClO decolorized the target product **1** and decomposed fluoro-vinyl **17** into water-soluble compounds (the double bond fluoro-vinyl **17** could be decomposed oxidatively by NaClO, forming polar water-soluble products). These two findings paved the way to a chemical purification of **10** and **1**. The goal was not to decompose **17** with KF but instead eliminate unreacted **9** immediately after the fluorination by means of selective hydrolysis with NaOH in H_2O/*n*-hexane. Keto-acid **21** was successively extracted into H_2O, while the other compounds remained in the *n*-hexane phase. After solvent exchange and hydrolysis with NaOH/

(27) Radhamani, K. N.; Padma, D. K. *J. Fluorine Chem.* **1993**, *64*, 95–99.
(28) Kalbandkeri, R. G.; Mohamed, K. S.; Padma, D. K.; Murthy, A. R. V. *Polyhedron* **1985**, *4*, 787–789.

Table 7. **Raw data from the fractional factorial experimental design**[a]



	→ Addition Order →							Fluorination Phase (% by HPLC)				Decomposition Phase (% by HPLC)			
Entry	**9** (mmol)	DCE (ml/mmol **9**)	DF (mol/mol **9**)	H_2O (mol/mol **9**)	$NaHCO_3$ (mol/mol **9**)	KF98% (mol/mol **9**)	PTC (mol/mol **9**)	**9**	**10**	**17**	Mss Balance	**9**	**10**	**17**	Mss Balance
1	26	0.0	1.6	0.1	0.2	2	0.1	53	39	11	102	8	21	9	38
2	17	0.0	3.0	0.1	0.2	1	0.1	46	38	11	94	40	37	0	77
3	17	0.7	1.6	0.1	0.2	1	0.1	60	33	7	100	53	35	7	95
4	12	0.7	3.0	0.1	0.2	2	0.1	48	41	10	99	42	45	1	88
5	27	0.0	1.6	0.3	0.6	1	0.1	56	36	9	101	38	33	9	79
6	17	0.0	3.0	0.3	0.6	2	0.1	44	44	12	100	33	42	4	78
7	17	0.7	1.6	0.3	0.6	2	0.1	76	26	5	106	61	25	4	90
8	12	0.7	3.0	0.3	0.6	1	0.1	36	43	13	92	28	47	1	76
9	27	0	1.6	0.1	0.2	0	0.1	52	35	10	97	39	34	6	80
10	17	0	3.0	0.1	0.2	0	0.1	44	41	11	96	38	44	0	82
11	17	0.7	1.6	0.1	0.2	0	0.1	62	34	7	104	51	31	7	89
12	12	0.7	3.0	0.1	0.2	0	0.1	51	43	10	104	40	42	0	82
13	26	0.0	1.6	0.3	0.6	0	0.1	56	35	10	100	41	16	9	66
14	17	0.0	3.0	0.3	0.6	0	0.1	42	48	13	103	27	39	2	68
15	17	0.7	1.6	0.3	0.6	0	0.1	70	23	4	97	67	27	4	99
16	12	0.7	3.0	0.3	0.6	0	0.1	45	44	12	100	37	45	11	93
17	17	0.3	2.3	0.2	0.4	1.4	0.1	47	40	11	98	38	40	10	87
18	17	0.3	2.3	0.2	0.4	1.4	0.1	46	43	11	100	44	36	6	85

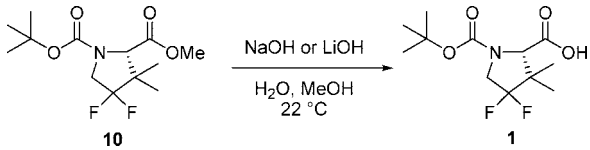
[a] The column "addition order" indicates the operation order required for the best results: $NaHCO_3$, KF, and PTC are added to the reaction mixture after 5 h of fluorination. Addition of KF and PTC in the fluorination step led to complete decomposition of **9**. In the last two columns, the results after fluorination (5 h, 70 °C) and selective decomposition of residual impurities (5 h, 70 °C), respectively, are collated. While the mass balance for the fluorination was near 100% by HPLC assay, the mass balance of the decomposition phase decreased as a result of the conversion of fluorovinyl **17** into more polar by-products that were extracted with water. Entry 10 shows the best operating conditions.

MeOH (according to Table 9, entry 5), **18** and the DF-related by-product were extracted into toluene, while product **1** and fluoro-vinyl impurity **22** remained in the aqueous phase, which in turn was treated with NaClO. After oxidation of the fluoro-vinyl **17** impurity, final product **1** was isolated by filtration from water, after adjustment to pH 2.5, in the presence of *n*-hexane to avoid gumming. This new procedure was implemented in production; a significant contribution to simplification of the overall process. The overall yields from **9** to **1** ranged from 39% to 42%, and the quality of **1** was high (HPLC assay 94–99%, 100% ee).

Conclusion

The original process for the production of **1** consisted of nine steps, which included an enzymatic resolution as the last transformation. The main drawbacks of this route were the late optical resolution; the use of toxic and hazardous reagents, solvents, and conditions ($ZnCl_2$, CH_3I, Pyr·SO_3/DMSO, MTBE, DF at 70 °C for 4 days); and the necessity of chromatographic purification of **10**. Moreover, the overall yield was very low (1.5%), despite careful manipulation of materials (estimated at about 7 t/kg of **1**). A new synthetic strategy, based on an early classical optical resolution, was evaluated and enabled. The early resolution halved the material to be processed in the later steps of the route. Toxic and hazardous reagents ($ZnCl_2$, MeI, Pyr·SO_3/DMSO) were avoided wherever possible, and in the case of DF, safer and faster conditions were established (the reaction time was decreased from 4 days to 5–10 h, thus reducing the risk associated with the heating a thermally sensitive reagent). The chromatographic purification of the crude **10** was substituted with a practical chemical purification, which was based upon different reaction rates of **9** with respect to **10**, **17**, and **18**, during the final step, and the ability of NaClO to selectively decompose impurity **22** into water-soluble by-product. MTBE was eliminated from the process and was substituted with toluene for reactions and with water for the

Table 8. **Screening of base, concentration, and quantity of methanol for the hydrolysis of 10**



10 **1**

entry	aqueous base	base (equiv)	MeOH (mL/g **10**)	time (h)	yield (%)
1	8% NaOH	6	17	96	100
2	20% NaOH	6	17	24	100[a]
3	8% LiOH	6	17	96	<50
4	8% NaOH	2	17	96	46
5	8% NaOH	4	17	96	87
6	8% NaOH	6	0	96	11
7	8% NaOH	6	4	96	100
8	8% NaOH	6	10	96	100

[a] 7% Racemization occurred.

Table 9. **Summary of the manufacturing campaign of 1**

product	batch size (kg)	av batch size (kg)	reactor volume (L)	no. of batches	quantity (kg)
2	n.a.	n.a.	n.a.	n.a.	103
3	30	20.6	250	5	129
4	13.5	11.7	170[a]	11	87
salt p	10	8.7	250	8	62
salt p purified	14	12.4	250	5	54
6	27	13.5	250	4	35
8	17.5	17.5	250	2	29
9	12.9	9.7	250	3	26
10	3.5	2.6	35[b]	10	11
1	2.7	2.2	100	5	7.5

[a] Cryogenic reactor. [b] Halar-coated reactor.

crystallization of **4** and **1**. It was discovered that the Ireland−Claisen rearrangement of **3** to **4** could be efficiently executed in the absence of Lewis acid. The stereochemical pathway for the basic rearrengement of **6b** was elucidated, which led to control of the configuration of the α-carbon. A safe, environment-friendly, and reliable oxidation of **8** to **9** with NaOCl/TEMPO was employed. Finally it was discovered that silica gel promoted the DF-mediated fluorination of ketone **9**.

These improvements resulted in a reliable and safe process. The overall yield from **2** to **1** increased about 300% (from 1.5% to 4.5%), while the major improvements were obtained for the transformation of **4** to **8** (from 33% to 73%) and for the oxidation of **8** to **9** (from 64% to 95%). These yield improvements resulted in the reduction of all materials used in the process from 7 t/kg of **1** to less than 2 t/kg of **1**.

The successful scaling of this process in the plant gave 7.5 kg of **1**. The campaign was conducted with glass-lined 250-L, cryogenic 170-L, and Halar-coated 35-L reactors (Table 9). The number of batches per single step ranged from 3 to 11, while the entire campaign lasted about 6 months.

Experimental Section

Instrumentation and Materials. *^{1}H NMR.* Varian 400 or 500 MHz spectrometer chemical shifts (δ values) are reported

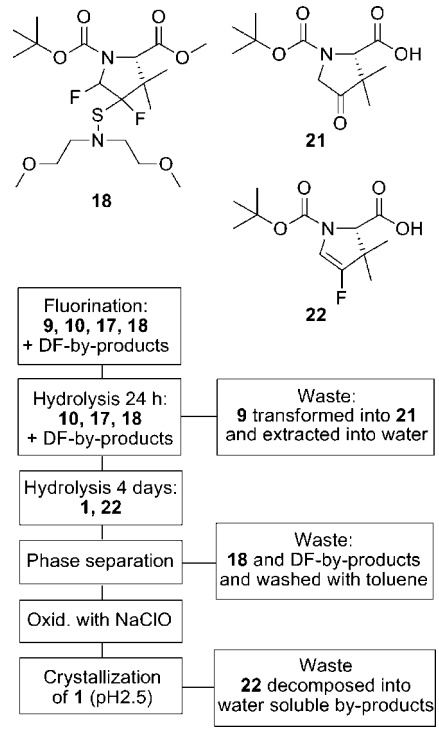


Figure 8. **Diagram for the chemical purification of 10 and 1. Decomposition of 17 could be postponed until after the saponification of 10 and 17 to 1 and 22, respectively, and was thus performed with NaClO instead of KF and PTC. The main advantage of such a modification is the reduction of residence time in the Halar reactor; as a result of the small reactor volume (maximum 35 L), 10 fluorination batches were required to convert all of ketone 9 to 10. While the decomposition of 17 with KF must be done in the Halar reactor, decomposition of 22 with NaClO could be accomplished in larger glass or glass-lined reactors. The latter option permitted the combination of several batches, provided that the residual DF was quenched with aqueous NH_4OH before the NaClO decomposition process. This simplified procedure allowed isolation of pure 1 without chromatographic purification and with no decrease in yield.**

in ppm based on tetramethylsilane (δ = 0 ppm), coupling constants (*J*) (H, H) are given in Hz, spectral splitting pattern are designated as singlet (*s*), doublet (*d*), triplet (*t*), quadruplet (*q*), multiplet or overlapping signals (*m*), broad signal (*br*), solvent is given in parentheses.

^{13}C NMR. Varian 100 or 125 MHz spectrometer chemical shifts (δ values) are reported in ppm based on tetramethylsilane (δ = 0 ppm), all spectra are proton broadband decoupled, multiplicities of the signals were determined by DEPT measurements, solvent is given in parentheses.

MS: LC-MS. HPLC-IONTRAP-MS: Agilent 1100 Series LC/MSD Trap VL.

ATR FTIR in Situ Spectroscopy. ReactIR 4000, Mettler Toledo, equipped with chemometric software, ConcIR from Mettler Toledo.

FC. Silica gel 60 (Fluka, 40–63 μm), air or mechanic pressure of ca. 0.2−3 bar, eluents are given in parentheses.

pH measurements. The solutions were pH tested at 25 °C with a digital Metrohm 632 pH meter that had been referenced to pH 7.00 and 4.00 with buffer standard solutions (CER).

Techniques. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under nitrogen.

Solvents. Toluene, MeOH, THF, CH_2Cl_2, EtOH, *n*-hexane, methyl alcohol, EtOAc, and 1,2-dichloroethane [CAUTION: carcinogenic substance. R45, 11, 22, 36/37/38; S53, 45] were purchased in pure grade quality (>99%) from Carlo Erba Reagenti.

Reagents and Substrates. LDA was purchased from Aldrich Chemical Co. or Chemetall as a 1.8 M THF solution; THF (NMT 0.05% H_2O). NaOH, H_2SO_4, TMSCl, $NaHCO_3$, Na_2CO_3 and K_2CO_3, and silica gel 60 230–400 mesh were purchased in *RPE* quality from Carlo Erba Reagenti. TEA, TBD, NaOMe and Boc_2O were purchased from Aldrich Chemical Co. Deoxo-Fluor [CAUTION: this reactive is potentially explosive, extremely flammable, reacts violently with water, is toxic if swallowed and causes severe burns. R35, 25, 2, 14, 11, 20; S9, 26, 33, 35, 36/37/39, 45] was purchased from Air Products (http://www.airproducts.com) as a 50 wt % solution in toluene, was stored at 4 °C, and was handled in dry conditions under nitrogen. Two types of KF were used: spray-dried material of 99% purity (abbreviated KF_{sd}) and nonspray-dried material of 98% purity (abbreviated $KF_{98\%}$) [CAUTION: mutagenic and teratogen substance, if decomposes may generate HF. Avoid strong acids. R23/24/25; S26, 45]. Aliquat 336 was purchased from Fluka, silica gel 60 (230–400 mesh) was purchased from CER, and all other reagents were obtained from Aldrich Chemical Co.

Statistical Analysis. Data was evaluated with MODDE, 7.0.0.1 software (Umetrics AB, Sweden) and Microsoft Excel 9.0 sofware.

Parallel Multireactor. Automated HEL Duet 317, manual Argonaut Quest 210.

Differential Scanning Calorimetry (DSC). Mettler Toledo DSc822 plus sample robot TSO801RO.

Calvet Calorimeter. Setaram C80D.

HPLC Analytical Methods. The following HPLC methods were developed for in-process control (ICP) and determination of chemical and optical purity of each product, intermediate, and by-product. Analysis of prepared compounds was performed on an Agilent HP1100 system equipped with a quaternary pump and a diode array detector (UV-PDA cell 10-mm path).

HPLC Method 1. Used for chemical purity and ICP of **1**, **3**, **4**, **5b**, **6b**, **8**, **9**, and **10**. Merck Symmetry C_{18} 5 μm column (4.6 × 250 mm); 27 °C chamber, 1.0 mL/min flow rate, 5 μL injection vol, 210 nm detection, 4 nm bandwidth. Phase A: 25 nM KH_2PO_4 adjusted to pH 2.5. Phase B: CH_3CN. Elution: isocratic 45% B from 0 to 4 min; linear gradient from 45% to 70% B from 4 to 15 min; isocratic 70% B from 15 to 25 min; linear gradient from 70% to 45% B from 25 to 30 min.

HPLC Method 2. Used for optical purity of **1**, **4**, **salt p**, **9**, and **10**. Chiralcel OJ-RH 5 μm column (0.46 × 15 cm) fitted with a Chiralcel OJ-RH precolumn (0.4 × 1 cm), 30 °C chamber, 0.6 mL/min flow rate, 10 μL injection vol, 205 nm detection, 4 nm bandwidth. Phase A: H_2O + 0.1% CF_3CO_2H. Phase B: CH_3CN+ 0.1% CF_3CO_2H. Elution: isocratic 75% A, 25% B.

HPLC Method 3. Used for optical purity of **5b**. Diacel Chiracel OJ-RH 5 μm column (4.6 × 250 mm), 35 °C chamber, 0.5 mL/min flow rate, 10 μL injection vol, 205 nm detection, 4 nm bandwidth. Phase A: *n*-heptane/EtOH 94:6. Elution: isocratic *n*-heptane/EtOH (94:6) for 60 min.

HPLC Method 4. Used for optical purity of **6b**. Diacel Chiracel OJ-RH 5 μm column (4.6 × 250 mm), 40 °C chamber, 0.5 mL/min flow rate, 5 μL injection vol, 205 nm detection, 4 nm bandwidth. Phase A: *n*-heptane. Phase B: 2-propanol. Elution: isocratic 40% B for 130 min.

HPLC Method 5. Used for optical purity of **8**. Diacel Chiracel OJ-RH 5-μm column (4.6 × 250 mm), 25 °C chamber, 0.5 mL/min flow rate, 10 μL injection vol, 205 nm detection, 4 nm bandwidth. Phase A: *n*-heptane/EtOH 93:7. Elution: isocratic 100% A for 35 min.

Preparation of *tert*-Butoxycarbonylamino-acetic Acid 3-Methyl-but-2-enyl Ester (3). EDC (715 g, 3.7 mol) was suspended in CH_2Cl_2 (1.2 L), which was then followed by addition of prenol (309 g, 3.6 mol) and DMAP (22.8 g, 0.19 mol). This suspension was stirred at 4−8 °C, and **2** (650 g, 3.71 mol) was then added over 2 h. The temperature was raised to 20 °C, and the solution was then washed sequentially with 5% aqueous $NaHCO_3$ (2 L), 0.5 N HCl (2 L), and H_2O (2 L). After distillation of the solvent, 841 g (95%) of **3** was obtained as an oily residue: 94.3% HPLC purity (t_R = 12.5 min), 96.6% HPLC assay, and 0.8% residual prenol (HPLC Method 1). Other analytical data are in accordance with the literature.[6]

Preparation of (±)-2-(2,2-Dimethyl-propionylamino)-3,3-dimethyl-pent-4-enoic Acid (*rac*-4). Compound **3** (50 g, 205.5 mmol) was dissolved in THF (170 mL) and was then cooled to −65 ± 5 °C under N_2. LDA (281 mL of a 1.8 M solution in THF, 514 mmol) was added to the solution of **3**, while maintaining the reaction temperature at −65 ± 5 °C (30 min required). After reacting for 1 h at −65 ± 5 °C, the mixture was warmed to 20 °C over about 20 min and was then maintained at 20 °C for about 1 h. Toluene (50 mL) was added, and the mixture was then cooled to 0 °C. The pH was adjusted to 2–3 with 10% aqueous H_2SO_4, and the phases were then separated. *rac*-**4** was extracted from the organic phase with 1 M NaOH (190 mL). *n*-Hexane (50 mL) was added to the resulting aqueous phase, and the mixture was stirred vigorously for 15 min and then cooled to −10 °C. The pH was adjusted to 2–3 with 20% aqueous H_2SO_4. Precipitated *rac*-**4** was filtered, washed with *n*-hexane, and then dried under house vacuum at 35–40 °C for 15 h to give 37 g (72%) of *rac*-**4** as a white solid: 93.7% HPLC purity (t_R = 9.2 min); 94.5% HPLC assay (HPLC Method 1); mp = 109.5 °C. Other analytical data are in accordance with the literature.[6]

Isolation of 2-(3,3-Diisopropyl-ureido)-3,3-dimethyl-pent-4-enoic Acid (11). This by-product of *rac*-**4** was isolated from the organic fraction and was purified by flash chromatography on silica gel (hexane/EtOAc 1:1, R_f = 0.3): t_R = 9.3 min (HPLC Method 1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.09 (s, 6H, $(CH_3)_2$-C-CH_2), 1.18 (d, J = 2.7 Hz, 6H, $(CH_3)_2$-CH-N), 3.90 (m, J = 6.9 Hz, 2H, $(CH_3)_2$-C*H*), 4.12 (d, J = 8.8 Hz, 1H, NH-C*H*), 4.87 (d, J = 8.8 Hz, 1H, N*H*-CO), 5.08 (dd, J = 17.5, 10.8 Hz, 2H, CH_2=CH), 5.92 (dd, J = 10.7, 6.7 Hz, 1H, CH_2=C*H*), 12.6 (s, 1H, COO*H*). MS (ion trap): $[C_{14}H_{26}N_2O_3 + H]^+$ 271.2, $[C_{14}H_{26}N_2O_3 + Na]^+$ 563.3.

Resolution of (±)-2-(2,2-Dimethyl-propionylamino)-3,3-dimethyl-pent-4-enoic Acid (*rac*-4) with (+)-(*S*)-Phenylgly-

cinol. *rac*-**4** (1.0 kg, 4.1 mol) was dissolved in CH_3CN/MeOH (9:1, 19 L), and (+)-(*S*)-phenylglycinol (560 g, 4.1 mol) was then added. The mixture was heated at reflux for 1 h and was then cooled to 20 °C over 20 h. The solid was filtered, washed with CH_3CN/MeOH (9:1, 0.8 L), and then dried at 40 °C for 20 h to give crude salt p (48% yield, 84% ee). Crude salt p was slurried in CH_3CN/MeOH (9:1, 15 L per kg of crude) at reflux for 1 h and was then cooled to 20 °C over 20 h. The solid was filtered, washed with CH_3CN/MeOH (9:1, 0.8 L), and dried at 40 °C for 20 h to give 670 g (43% overall yield) of pure salt p: 95.2% HPLC assay (HPLC Method 1); 96% ee [t_R (*S*)-**4** = 14.6 min, (*R*)-**4** = 13.1 min, HPLC Method 2]; mp 185.5 °C.

Preparation of 2-(2,2-Dimethyl-propionylamino)-3,3-dimethyl-pent-4-enoic Acid [(*S*)-4] by Hydrolysis of salt p. Salt p (809 g, 2.1 mol) was suspended in H_2O (3.8 L) and was then cooled to 5 °C. EtOAc (2.2 L) was added, and the temperature was readjusted to 5 °C. The pH was adjusted to 3.0 ± 0.5 with 10% aqueous HCl, while maintaining the internal temperature at <10 °C. The phases were separated and the aqueous phase was then extracted with EtOAc (485 mL). The EtOAc extracts were combined to afford a solution of (*S*)-**4** (quantitative yield) that can be directly used for the synthesis of **5b**.

Preparation of *cis*/*trans*-[(3*S*)-5-Bromometlyl-4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl]-carbamic Acid *tert*-Butyl Ester (5b). NBS (42 g, 234 mmol.) was suspended in EtOAc (261 mL), and the mixture was then cooled to 0 °C. A solution of (*S*)-**4** (51.8 g, 213 mmol) was added at a rate to maintain the internal temperature at 0 ± 5 °C. The reaction was quenched by addition of H_2O (170 mL), followed by Na_2SO_3 (6.5 g). The mixture was washed with 2% aqueous $NaHCO_3$ (170 mL), which afforded a solution of **5** (quantitative yield) that was directly used for the synthesis of **6b**. An analytical sample was prepared in 94% yield by crystallization from *n*-hexane: 90% HPLC assay; *cis*/*trans* ratio = 93:7 (t_R *cis*-**5b** = 12.5 min, t_R *trans*-**5b** = 12.2 min, HPLC Method 1); 96% ee [t_R (3*S*,5*S*)-**5b** = 19.3 min, t_R (3*R*,5*R*)-**5b** = 16.8 min, t_R (3*S*,5*R*)-**5b** = 26.6 min, t_R (3*R*,5*S*)-**5b** = 24.0 min, HPLC Method 3]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.69 (s, 3H, CH_3-C-CH), 1.07 (s, 3H, CH_3-C-CH), 1.40 (s, 9H, (CH_3)$_3$CO), 3.51 (dd, J = 11.5, 10.0 Hz, 1H, CH_2-CBr), 3.86 (dd, J = 11.5, 2.6 Hz, 1H, CH_2-CBr), 4.54 (dd, J = 10.0, 2.6 Hz, 1H, CH-CH_2Br), 4.60 (d, J = 9.8 Hz, 1H, CH-N), 7.40 (d, J = 9.8 Hz, 1H, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 15.1 (*C*H_3), 22.2 (*C*H_3), 28.1 [(*C*H_3)$_3$CO], 30.4 (*C*H_2), 43.8 [(CH$_3$)-*C*], 59.8 (N-*C*), 78.6 [*C*-(CH$_3$)$_3$], 84.3 (*C*-CHO), 155.8 [*C*O(CH$_3$)$_3$], 173.4 (*C*O_2CN). MS (ESI): [$C_{12}H_{20}BrNO_4$ + Na]$^+$ 345.9, [$C_8H_{12}BrNO_4$ + H]$^+$ 265.9, [$C_7H_{12}BrNO_2$ + H]$^+$ 224.0.

Preparation of (+)-(*S*)-3-Amino-5-bromomethyl-4,4-dimethyl-dihydro-furan-2-one (+)-(3*S*)-6b. The solution of **5b** in EtOAc prepared above was concentrated to 1 M and was measured by KF to contain ≤0.2 wt % H_2O. An equal volume of 4 M HCl/EtOAc was added in two portions over a period of at least 3 h, while maintaining the temperature at 20 ± 5 °C. The mixture was allowed to react for ≥10 h at 20 ± 5 °C and was then cooled to −10 °C for 2 h. The solid was filtered, and the solid was washed with *n*-hexane without mixing. After drying at 40 ± 5 °C under vacuum for ≥15 h, 50 g (91%) of **6** was obtained as a white solid: 97.4% HPLC purity; 92% HPLC assay; *cis*/*trans* ratio = 93:7 (t_R *cis*-**6b** = 12.5 min, t_R *trans*-**6b** = 12.2 min, HPLC Method 1); 96% ee [t_R (3*S*,5*S*)-**6b** = 19.3 min, t_R (3*R*,5*R*)-**6b** = 11.0 min, t_R (3*S*,5*R*)-**6b** = 91.2 min, t_R (3*R*,5*S*)-**6b** = 15.3 min, HPLC Method 4]; ^{1}H NMR (500 MHz, DMSO-d_6) *cis*-**6b** δ 0.90 (s, 3H, CH_3-C-CH), 1.34 (s, 3H, CH_3-C-CH), 3.64 (dd, J = 11.6, 9.9 Hz, 1H, CH_2-CBr), 3.99 (dd, J = 11.6, 2.3 Hz, 1H, CH_2-CBr), 4.39 (s, 1H, CH-N), 4.65 (dd, J = 10.0, 2.4 Hz, 1H, CH-CH_2Br), 8.95 (s, 3H, NH_3), *trans*-**6b** δ 1.13 (s, 3H, CH_3-C-CH), 1.29 (s, 3H, CH_3-C-CH), 3.64 (dd, J = 11.6, 9.9 Hz, 1H, CH_2-CBr), 3.99 (dd, J = 11.6, 2.3 Hz, 1H, CH_2-CBr), 4.45 (s, 1H, CH-N), 4.61 (dd, J = 9.4, 3.3 Hz, 1H, CH-CH_2Br), 8.95 (s, 3H, NH_3^+); ^{13}C NMR (100.6 MHz, DMSO-d_6) *cis*-**6b** δ 15.0 (*C*H_3), 22.8 (*C*H_3), 30.7 (*C*H_2), 44.3 [(*C*H_3)$_2$-*C*], 58.7 (N-*C*), 86.8 (*C*-CHO), 172.6 (*C*O_2CN), *trans*-**6b** δ 20.0 (*C*H_3), 22.3 (*C*H_3), 32.5 (*C*H_2), 41.5 [(CH$_3$)-*C*], 55.6 (N-*C*), 86.4 (*C*-CHO), 171.4 (*C*O_2CN). MS (ESI): [$C_7H_{13}BrNO_2$]$^+$ 222.0.

Preparation of (2*S*)-4-Hydroxy-3,3-dimethyl-pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (2*S*)-8. $NaHCO_3$ (16.2 g, 193 mmol) was suspended in MeOH (100 mL) at ambient temperature. Compound **6b** (50.0 g, 193 mmol) was dissolved in MeOH (150 mL), and the resulting solution was then added to the $NaHCO_3$ suspension while the internal temperature was at 20 ± 5 °C. The mixture was heated at reflux (65 ± 2 °C) for ≥17 h and was then cooled to 20 ± 5 °C. A solution of Boc_2O (50.7 g, 232 mmol) and NEt_3 (26.9 mL, 193 mmol) was added, and the mixture was then stirred at 20 ± 5 °C for ≥1 h. The reaction mixture was concentrated to one-third of the volume, toluene (210 mL) was added, and the mixture was then washed with H_2O (2 × 170 mL). The organic phase was concentrated under vacuum (50−100 mbar) at 40 ± 5 °C to give a 50 wt % solution of **8**. *n*-Hexane (350 mL) was added at 40 ± 5 °C, and the solution was then slowly cooled to 20 ± 5 °C. After crystallization, the suspension was stirred at −10 °C for 2 h and was then filtered. The solid was washed with *n*-hexane (50 mL) and was then dried at 35 ± 5 °C for ≥18 h to give 42.2 g (80%) of **8** as a white solid: 93% HPLC purity; *cis*/*trans* ratio = 90:1 [t_R *cis*-(2*S*)-**8** = 6.4 min, t_R *trans*-(2*S*)-**8** = 6.0 min, HPLC Method 1]; 100% ee [t_R (3*S*,5*S*)-**8** 14.7 min, t_R (3*R*,5*R*)-**8** 13.7 min, t_R (3*S*,5*R*)-**8** 17.8 min, t_R (3*R*,5*S*)-**8** 16.1 min, HPLC Method 5]; mp 87.4 °C; ^{1}H NMR (500 MHz, DMSO-d_6) *cis*-(2*S*)-**8** δ 0.78 (*s*, 3H, CH_3-C-CH), 1.11 (*s*, 3H, CH_3-C-CH), 1.33 and 1.41 rotamers [*s*, 9H, (CH_3)$_3$-CO], 3.03–3.10 (m, 1H, CH_2-N), 3.57 – 3.83 (m, 1H, CH_2-N), 3.65 (s, 3H, CH_3O), 3.78–3.82 (m, 1H, CH-OH), 3.87 (s, 1H, CH-COOCH$_3$), 5.18 (d, J = 5.02 Hz, 1H, CH-OH); ^{13}C NMR (100.6 MHz, DMSO-d_6) *cis*-(2*S*)-**8** mixture of rotamers δ 16.8 and 16.9 (*C*H_3), 25.0 and 25.2 (*C*H_3), 27.8 and 28.0 [(*C*H_3)$_3$-CO], 43.6 and 44.5 (*C*H-OH), 50.3 and 51.0 (*C*H_2), 51.3 and 51.4 (*C*H_3O), 67.0 and 67.4 (*C*H-CO_2CH_3), 74.2 and 74.9 (*C*H-OH), 78.9 and 79.0 [*C*-(CH$_3$)$_2$], 153.0 and 153.7 [*C*O-C(CH$_3$)$_3$], 170.3 and 170.9 (*C*O). MS (ESI) [$C_{13}H_{23}NO_5$ + H]$^+$ 273.7, [$C_9H_{15}NO_5$ + H]$^+$ 217.8, [$C_8H_{15}NO_3$ + H]$^+$ 174.1.

Isolation of 7,7-Dimethyl-3-oxo-2-oxa-5-aza-bicyclo[2.2.1]-heptane-5carboxylic Acid *tert*-Butyl Ester (13). Isolated from the organic phase in the synthesis of **8** and purified by flash

chromatography on silica gel (*n*-hexane/EtOAc 75:25 → 70:30): t_R 10.0 min (HPLC Method 1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.39 [s, 9H, (CH_3)$_3$], 3.20 (d, J = 11.4 Hz, 1H, CH_2), 3.54 (br d, J = 11.4, 1H, CH_2), 4.08 (br s, 1H, C*H*-N), 4.67 (s, 1H, C*H*-O); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 17.3 (*C*H$_3$), 17.6 (*C*H$_3$), 27.8 [(*C*H$_3$)$_3$C], 48.1 [*C*(*C*H$_3$)$_2$], 48.8 (*C*H$_2$), 65.3 (*C*H-N), 80.1 [*C*(CH$_3$)$_3$)], 84.2 (*C*H-O), 154.0 [*C*OC(CH$_3$)$_3$], 172.8 (*C*O). MS (ion trap) [$C_{12}H_{19}NO_4$]$^+$ 241.28.

Preparation of 3,3-Dimethyl-4-oxo-pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (9). A mixture of **8** (300 g, 1.1 mol), TEMPO (1.7 g, 9.1 mmol), KBr (1.7 g, 17.2 mmol), $NaHCO_3$ (83.4 g, 1.0 mol), and CH_2Cl_2 (1670 mL) was cooled to 0 °C. NaClO (1.8 L of a 5% aqueous solution) was added over 70 min, while maintaining the reaction temperature at <7 °C. The solution was stirred vigorously at 3 °C for 60 min. The resulting phases were separated, and the aqueous fraction was then extracted with CH_2Cl_2 (500 mL). The combined CH_2Cl_2 phases were sequentially washed with 5% aqueous $Na_2S_2O_5$ (1.8 L) and H_2O (1.8 L). The resulting CH_2Cl_2 solution was filtered to remove residual salts and was then evaporated to give 299 g (100%) of **9** as an oil: 97% HPLC purity; 99% HPLC assay (t_R 12.1 min, HPLC Method 1); 100% ee [t_R (2*S*)-**9** 25.2 min, t_R (2*R*)-**9** 22.8 min, HPLC Method 2]; ^{1}H NMR (500 MHz, DMSO-d_6) mixture of rotamers δ 0.96 (s, 3H, CH_3-C-CH), 1.24 and 1.25 (s, 3H, CH_3-C-CH), 1.40 and 1.45 [s, 9H, (CH_3)$_3$-CO], 3.68 and 3.72 (s, 3H, CH_3O), 3.82 (d, J = 18.6 Hz, 1H, CH_2-N), 4.09 (d, J = 18.9 Hz, 1H, CH_2-N), 4.35 and 4.38 (s, 1H, C*H*-COOCH$_3$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 18.2 (*C*H$_3$), 24.7 (*C*H$_3$), 27.8 [(*C*H$_3$)$_3$C], 49.3 [*C*(CH$_3$)$_2$], 50.9 (*C*H$_2$), 52.0 (*C*H$_3$O), 67.4 (*C*H-CO$_2$CH$_3$), 81.0 [*C*-(CH$_3$)$_3$], 172.2 (*C*OOCH$_3$), 212.8 (*C*O). MS (ESI): [$C_{14}H_{22}NO_5$+ H]$^+$ 271.6; [$C_{10}H_{14}NO_5$ + H]$^+$ 215.8.

Preparation of (*S*)-4,4-Difluoro-3,3-dimethyl-pyrrolidine-1,2-dicarboxylic Acid 1-tert-Butyl Ester 2-Methyl Ester (10). CAUTION: Avoid the use of acid in the presence of Deoxo-Fluor and KF to prevent evolution of HF (g). Ketone **9** (50 g, 184 mmol) was charged into a PTFE- or Halar-coated reactor at 23 °C and was then followed by the addition silica gel (2.5 g). Deoxo-Fluor (244.7 g of a 50 wt % solution in toluene, 552.9 mmol) was *slowly* added. The resulting mixture was heated to 70 ± 2 °C and was then stirred at this temperature for 5–10 h. $NaHCO_3$ (3.1 g, 37 mmol), KF (10.7 g, 184 mmol), and Aliquat 336 (8.4 mL, 18.4 mmol) were added at 70 °C, and the mixture was allowed to stir at 70 °C for an additional 5–24 h. The mixture was cooled to 23 °C and was then quenched in 10% aqueous NH_4OH (425 mL) while the pH was maintained around 8.5. The organic phase was separated and was then washed with H_2O (425 mL). Evaporation of the organic phase, followed by flash chromatography on silica gel (*n*-hexane/EtOAc 30:1 → 10:1.5), gave 25.4 g (47%) of **10** as an oil: 98% HPLC purity; 97% HPLC assay (t_R 16.1 min, HPLC Method 1); 100% ee (t_R (2*S*)-**10** 51.7 min, t_R (2*R*)-**10** 43.6 min, HPLC Method 2); ^{1}H NMR (500 MHz, DMSO-d_6) mixture of rotamers δ 1.01 (s, 3H, CH_3-C-CH), 1.25 (s, 3H, CH_3-C-CH), 1.36 and 1.43 [s, 9H, (CH_3)$_3$-CO], 3.70 and 3.73 (s, 3H, CH_3O), 3.87 (dd, J = 26.0, 12.48 Hz, 2H, CH_2-N), 4.10 (s, 1H, C*H*-COOCH$_3$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 16.9 (*C*H$_3$), 20.8 (*C*H$_3$), 27.5 [(*C*H$_3$)$_3$C], 45.1 [*C*(CH$_3$)$_2$], 50.3 (*C*H$_2$), 51.4 (*C*H$_3$O), 66.8 (*C*H-CO$_2$CH$_3$), 80.0 [*C*-(CH$_3$)$_3$], 126.3 (*C*F$_2$), 152.7 [*C*OC(CH$_3$)$_3$], 169.8 (*C*OOCH$_3$). MS (ESI): [$C_9H_{13}F_2NO_4$ + H]$^+$ 237.8, [$C_8H_{13}F_2NO_2$ + H]$^+$ 194.0, [$C_6H_{11}F_2N$ + H]$^+$ 134.1.

Isolation of 4-Fluoro-3,3-dimethyl-2,3-dihydro-pyrrole-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methylester (17). Isolated in the synthesis *rac*-**4** and purified by flash chromatography on silica gel [hexane/EtOAc 4:0.1 → 3:7; R_f = 0.7 hexane/EtOAc (1:2)] to give an oil: t_R 16.9 min (HPLC Method 1); ^{1}H NMR (500 MHz, 70 °C, DMSO-d_6) δ 1.01 (s, 3H, CH_3-C-CH), 1.36 (s, 3H, CH_3-C-CH), 1.42 [s, 9H, (CH_3)$_3$-CO], 3.75 (s, 3H, CH_3O), 4.31 (s, 1H, C*H*-COOCH$_3$), 6.51 (s, 1H, C*H*-CF$_2$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 21.7 (*C*H$_3$), 26.3 (*C*H$_3$), 27.8 [(*C*H$_3$)$_3$C], 52.0 (*C*H$_3$O), 69.2 (*C*H-CO$_2$CH$_3$), 108.9 (*C*H-CF$_2$). MS (ESI) [$C_9H_{12}FNO_4$ + H]$^+$ 217.8; [$C_8H_{12}FNO_2$ + H]$^+$ 173.9; [C_6H_8FN + H]$^+$ 114.0.

Isolation of *N*-[*N*,*N*-Bis(2-methoxy-ethyl)-aminosulfanyl]-4,5-difluoro-3,3-dimethyl-pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (18). Isolated in the synthesis *rac*-**4** and purified by flash chromatography on silica gel (hexane/EtOAc 1:0 → 2:1; R_f = 0.3 hexane/EtOAc 1:2) to give **18** as a mixture of diastereomers: t_R 21.0, 21.3 min (HPLC Method 1); ^{1}H NMR (500 MHz, DMSO-d_6) mixture of diastereomers δ 0.97 and 1.07 (s, 3H, CH_3-C-CH), 1.1.8 and 1.25 (s, 3H, CH_3-C-CH), 1.45 [s, 9H, (CH_3)$_3$-CO], 3.23–2.21 (m, 2H, CH$_3$O-CH$_2$-CH_2-N), 3.29 (s, 3H, CH_3O-CH$_2$-CH$_2$-N), 3.51 (t, J = 5.97, 2H, CH$_3$O-CH_2-CH$_2$-N), 3.75 (s, 3H, CH_3O), 4.19 and 4.21 (s, 1H, C*H*-COOCH$_3$), 5.98 (d, J = 5.97, 1H, F-C*H*); ^{13}C NMR (125 MHz, 70 °C, DMSO-d_6) mixture of diastereomers δ 19.9 (*C*H$_3$), 21.8 (*C*H$_3$), 28.5 [(*C*H$_3$)$_3$C], 47.1 [*C*(CH$_3$)$_2$], 52.4 (*C*H$_3$O), 58.7 (*C*H$_3$O-CH$_2$), 60.0 (N-*C*H$_2$), 69.8 (*C*H-CO$_2$CH$_3$), 71.3 (*C*H$_2$-O), 83.0 [*C*-(CH$_3$)$_3$], 153.8 [*C*OC-(CH$_3$)$_3$], 169.8 (*C*OOCH$_3$). MS (ESI) [$C_{19}H_{34}F_2N_2O_6S$ + Na]$^+$ 479.0; [$C_{19}H_{33}FN_2O_6S$ + H]$^+$ 436.9; [$C_{14}H_{25}FN_2O_4S$ + H]$^+$ 336.9.

Preparation of 4,4-Difluoro-3,3-dimethyl-pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester (1) without Chromatography. CAUTION: Avoid the use of acid in the presence of Deoxo-Fluor and KF to prevent evolution of HF (g). Ketone **9** (50 g, 184 mmol) was charged into a PTFE- or Halar-coated reactor at 23 °C, which was then followed by the addition of silica gel (2.5 g). Deoxo-Fluor (244.7 g of a 50 wt % solution in toluene, 552.9 mmol) was *slowly* added. The resulting mixture was heated to 70 ± 2 °C and was then stirred at this temperature for 5–10 h. The mixture was cooled to 23 °C and was then quenched in 10% aqueous NH_4OH (425 mL) while the pH was maintained around 8.5. The organic phase was separated and was then washed with H_2O (425 mL). The solvent was distilled under vacuum to give a mixture of **9** and **10** as an oil, which was then dissolved in *n*-hexane (133 mL). NaOH (2 N, 154 mL) was added, and the resulting biphasic mixture was agitated at 23 °C for about 24 h until no residual **9** remained in the organic phase. The layers were separated, and the organic phase was concentrated under vacuum to give crude **10** as an oil. The residue was dissolved in MeOH (255 mL), and 2 N NaOH (255 mL) was then added. After stirring for 4 days at 23 °C, the solution was adjusted to ~pH 7 with 10% aqueous

HCl. The organic solvent was distilled off under vacuum. The resulting aqueous solution was diluted with H_2O (100 mL) and was then washed with toluene (2 × 175 mL). The pH was adjusted to 12.5 with 10% aqueous NaOH, and NaOCl (31 mL of a 3.5 wt % aqueous solution) was then added. The resulting mixture was stirred at 23 °C until **17** no longer remained (2 h required). *n*-Hexane (75 mL) was added to the mixture, and **1** was then precipitated by adjustment to pH 2.5 with 10% aqueous HCl. The solid was filtered, washed with water, and dried to give **1** in 38–45% yield from **9** (45–50% for the fluorination and 85–95% for hydrolysis): 96% HPLC purity; 97% HPLC assay (t_R 9.2 min, HPLC Method 1); 100% ee [t_R (2*S*)-**1** 14.1 min, t_R (2*R*)-**1** 13.2 min, HPLC Method 2]; ^{1}H NMR (500 MHz, DMSO-d_6) mixture of rotamers δ 1.06 (s, 3H, CH_3-C-CH), 1.24 (s, 3H, CH_3-C-CH), 1.38 and 1.43 [s, 9H, (CH_3)$_3$-CO], 3.80 (dd, J = 25.7, 13.2, 2H, CH_2-N), 3.98 (s, 1H, C*H*-CO_2CH_3), 12.97 (s, 1H, COO*H*); ^{13}C NMR (75 MHz, DMSO-d_6) mixture of rotamers δ 17.7 and 17.9 (*C*H_3), 21.4 and 21.6 (*C*H_3), 28.1 and 28.3 [(*C*H_3)$_3$C], 44.9 and 45.6 [*C*(CH_3)$_2$], 51.0 and 51.5 (*C*H_2), 67.3 and 67.8 (*C*H-CO_2CH_3), 80.3 and 80.8 [*C*-(CH_3)$_3$], 126.8 and 127.3 (*C*F_2), 153.3 and 153.7 [*C*OC(CH_3)$_3$], 170.3 and 170.8 (*C*OOH). MS (ESI) [$C_8H_{11}F_2NO_4$ + H]$^+$ 223.9; [$C_7H_{11}F_2NO_2$ + H]$^+$ 180.0; [$C_6H_9F_2N$ + H]$^+$ 134.1.

Acknowledgment

This work could not have been done without the important contribution of many colleagues. We are thankful to C. Brusamolino, I. Colombo, A. Re, L. Biagini, and M. De Pietro for analytical support; G. Ottainano, G. Mandirola, S. Capezzera, P. Leonetti, D. Mercuri, and Franco Rossi for production operations; M. Ungari for hazard evaluation; and A. Adduci and C. Lista for lab support.

Received for review May 22, 2007.

OP7001112