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A Practical Synthesis of the Dual Matrix Metalloprotease/Tumor Necrosis Factor Inhibitor MMP090

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Abstract:

A practical 9-step synthesis of the dual matrix metalloprotease/tumor necrosis factor inhibitor MMP090, *trans*-(*R*)-[[*N*-(4-ethoxyphenylsulfonyl)-*N*-(4-pyridinylmethyl)]amino]-*N*-hydroxy-4-propoxy cyclohexaneacetamide 10, was accomplished in 12% overall yield from D-4-hydroxyphenylglycine. Highlights include: (1) selective hydrogenation of D-hydroxyphenylglycine to afford predominantly the trans isomer without racemization; (2) virtually complete removal of the undesired cis diastereoisomer by fractional recrystallization of a TBS ether derivative of the functionalized cyclohexylglycine; (3) direct conversion of the TBS ether into the *n*-propyl ether in the presence of a catalytic amount of bismuth bromide in high yield; and (4) conversion of the carboxylic acid into the hydroxamic acid using an aqueous solution of hydroxylamine.

1. Introduction

Matrix metalloprotease (MMP) inhibitors are currently being developed for the treatment of rheumatoid arthritis and osteoarthritis, and they have high clinical attractiveness due to their ability to slow or even halt the progression of arthritis. Extensive work on the medicinal aspects of these compounds has been reported.[1] The preparation of some of the compounds currently in development has also been described.[2] In this paper we report a practical and convergent synthesis of the clinical candidate MMP090, a dual MMP/tumor necrosis factor (TNF) inhibitor recently identified by the Novartis Drug Discovery group.[3]

Structurally, MMP090 is a highly functionalized, reduced hydroxyphenylglycine derivative in which the cyclohexyl oxygen is alkylated with an *n*-propyl group and the nitrogen is alkylated and sulfonylated. The original 12-step synthesis[3] of MMP090 was designed to provide a route to a wide variety of structurally related compounds (Scheme 1). In assessing the viability of this route for scale-up purposes, several problems became apparent. In the preparation of the sulfonyl chloride **2**, the potential existed for the buildup of thionyl chloride in the reaction mixture as the scale increases, resulting in the subsequent rapid evolution of HCl and SO_2. The Raney nickel reduction of **3** was hampered by low throughput and tedious product isolation, as well as reaching a trans/cis selectivity of only about 3:1. The preparation of the benzyl ester **6** was also a low-throughput process, and in addition, the product was contaminated with 3−5% of dicyclohexylammonium bromide. This contaminant interferes with the oxidation in the next step such that additional quantities of oxidant were required. The reductive alkylation (**Step 7 → 8**) could not be scaled up in the pilot plant since it was considered operationally dangerous due to the high reactant concentrations, the exothermicity of the reaction, as well as the high viscosity of the reaction mixture. All attempts to change the conditions shut down the reaction completely. In addition, approximately 30% of **7** was lost via the formation of trifluoroacetate esters. The isolated product **8** was a 3:1 mixture of diastereoisomers (trans predominating) which required chromatography for purification.

In addition, we found that 3−7% of **8** had undergone racemization due to the strongly acidic reaction conditions. Multiple recrystallizations were required in order to obtain acceptable material. The actual yield after purification was only 22% for this step. For the preparation of **9** we found that an impurity from the alkylation step (either 4-picolyl chloride or a polymeric derivative) acted as a catalyst poison thus requiring additional quantities of catalyst after the reaction had stalled. Finally, we found that the free base of MMP090 was not a solid, thus making purification of the penultimate intermediate extremely difficult. These problems provided severe limitations to the use of this chemistry for large scale preparation.

After considering several alternative routes and comparing them with the original synthesis, it was decided that the latter was still the most attractive for the initial scale-up, providing the following criteria could be met:

(i) the selectivity of the Raney nickel reduction (**3 → 4**) should remain unchanged or improve on larger scale;

(ii) conditions would need to be identified for the O-alkylation of **6** which are safe and efficient;

(iii) the chromatographic purification to remove the cis isomer should be eliminated;

(iv) an effective method for the preparation of the hydroxamic acid could be identified.

Scheme 2 summarizes our efforts to improve the synthesis and to circumvent the major problems. Specifically, by combining good selectivity in the Raney nickel reduction with fractional crystallization of an advanced intermediate, we were able to eliminate the undesired cis isomer from the final product. In addition, we developed a new catalytic

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(1) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305. Hagmann, W. K.; Larkk, M. W.; Becker, J. W. *Annu. Rep. Med. Chem.* **1996**, *31*, 231.

(2) Wojtowicz-Praga, S. *Drugs in R&D* **1999**, *1*, 117.

(3) Parker, D. T. (Novartis) U.S. Patent 5,770,624, 1998.

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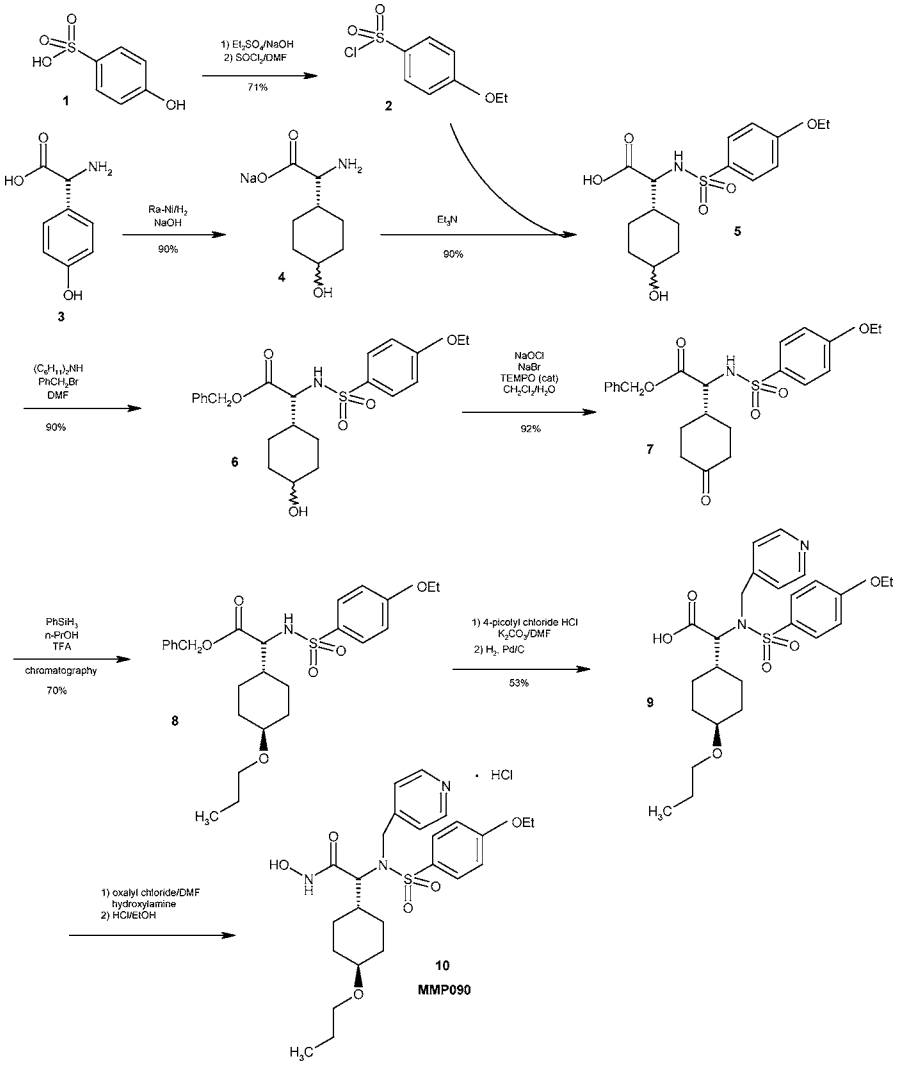
Scheme 1. **Original 12-step synthesis of MMP090**



procedure for the reductive alkylation of secondary alcohols which allowed for an efficient preparation of ether **8**.

Our efforts, which culminated in the successful realization of the above strategy for the preparation of MMP090, are outlined below.

2. Results and Discussion

(*R*)-α-[*N*-(4-Ethoxyphenylsulfonyl)amino]-4-hydroxycyclohexaneacetic Acid (5). The sodium salt of the sulfonic acid was O-alkylated using diethyl sulfate in a basic aqueous medium. The product (isolated as the sodium salt) was converted to the sulfonyl chloride **2** using a mixture of thionyl chloride/DMF in toluene. The original process was modified in that the sulfonyl chloride was added slowly to a hot (78 °C) solution of the substrate in toluene/DMF. This addition-controlled procedure allowed for moderation of the gas evolution as well as the heat of the reaction. Although crystalline, it was easier to handle compound **2** as a toluene solution. The overall yield for the two steps was 65%.

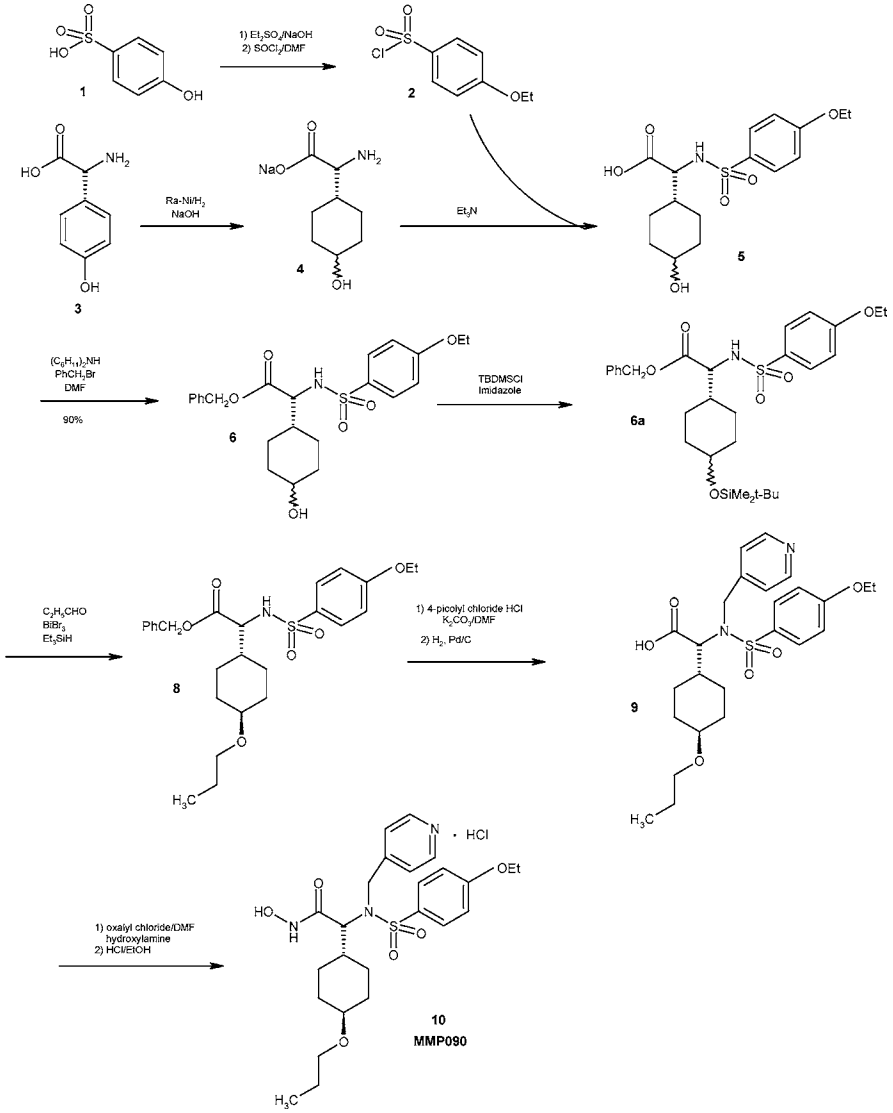
We next turned our attention to the reduction of D-hydroxyphenylglycine **1**. The original hydrogenation conditions involved the use of excess Raney Nickel in aqueous base at elevated temperature (50−70 °C) to effect the reaction.[3−5] The maximum trans/cis ratio of **4** found under these conditions was 3.2/1[6] (no information with regard to the trans/cis ratio of the cyclohexylglycine is given in refs 4 and 5).

Although the conversion of the starting material was >95%, analysis of the crude reaction mixture by NMR revealed that hydrogenolysis of the hydroxyl group had also taken place.[5] Cleavage of the amino group may also have occurred under these conditions.[7,8] In addition, there was concern regarding the partial racemization of the substrate during the hydrogenation, since this had been observed under certain conditions in the case of (*R*)-phenylglycine.[7]

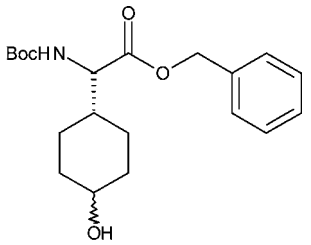
Initially, our efforts were directed towards the separation of the trans/cis mixture of reduction products **4** since it had

(4) Blaha, K.; Farag, A. M.; Van Der Helm, D.; Hossain, N. B.; Budesinsky, M.; Malon, P.; Smolikova, J.; Tichy, M. *Collect. Czech. Chem. Commun.* **1984**, *49*, 712.
(5) Edelson, J.; Fissekis, J. D.; Skinner, C. J.; Shive, W. *J. Am. Chem. Soc.* **1958**, *80*, 2698.
(6) Since it proved difficult to isolate **4** from the aqueous solution for analysis, an NMR method was developed to determine the trans/cis ratio. This involved the comparative integration of the cyclohexyl ring proton −C*H*(OH) (see Experimental Section).
(7) Tamura, M.; Harada, K. *Synth. Commun.* **1978**, *8*, 345.
(8) Minnaard, A. J.; Boesten, W. H. J.; Zeegers, H. J. M. *Synth. Commun.* **1999**, *29*, 4327.

Scheme 2. **Revised synthesis of MMP090**



been demonstrated in the literature that it was possible to accomplish this on the corresponding Boc benzyl ester **11**.[9]



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Thus a variety of functionalized derivatives of **3** were prepared and subjected to hydrogenation using several different catalysts and conditions. We found that substitution at the carboxyl group (i.e., esters) slowed the rate of reaction and only afforded a 2:1 trans/cis mixture of diastereoisomers regardless of the substituents present on the nitrogen and oxygen functionalities. Furthermore, the same was found to be the case for the N−CBZ and O-alkylated ethers. This was true regardless of the catalyst system used (Raney nickel, Rh/alumina, or Pt/C).

While this investigation was proceeding, it was discovered that the trans/cis isomer ratio could be improved to >120/1 in a later step by fractional recrystallization of **6a** (see below). Thus, it was decided to convert the mixture of the diastereoisomers **4** to the sulfonamides **5** and carry out the isomer separation at the later stage. Compound **5** was prepared by treating the aqueous solution of **4** with the sulfonyl chloride **2** in a mixture of triethylamine/acetonitrile. The reaction mixture was concentrated and extracted with ethyl acetate to remove organic impurities, and the product **5** was precipitated from the aqueous phase by acidification. The trans/cis ratio at this point was approximately 4/1.

With this result in hand, we focused our attention on improving the trans/cis ratio to the greatest extent practicable for the hydrogenation of **3** and also determining the amount of racemization (if any) during this process.

A review of the literature revealed that although less reactive than the common hydrogenation catalysts (e.g., Pd, Pt, Rh, and Ru) for the reduction of carbocyclic aromatic

(9) Banfi, A.; Benedini, F.; Sala, A. *Synth. Commun.* **1990**, *20*, 3585.

Table 1. **Step 3 → 4: screening of reaction conditions**[a]

ref	catalyst	base (equiv)	H_2 press. (psi)	temp (°C)	time (h)	conv (%)[b]	cis/trans
-31	RaNi	NaOH (2)	50	40	20	41.5	1/2
-35	RaNi	NaOH (1)	56	50−70	16	98.4	1/3.2
-38	RaNi	K_2CO_3 (1)	50	55	15	98.4	1/2.7
-43	RaNi	NaOH (0.8)	22	55	22	96.5	1/3.8
-44	RaNi	NaOH (0.8)	55	55	22	>99	1/3.7
-47	RaNi	NaOH (0.8)	22	75	20	94	1/4.3
-52	RaNi	NaOH (0.8)	10	80	18	90	1/5
-58	RaNi	NaOH (0.8)	17	90	19	93	1/6
-59	RaNi	NaOH (1)	17	90	18	94	1/5.5
-60	RaNi	NaOH (1)	17	100	4		
			48	70	15	61	1/5
-62	RaNi	NaOH (0.8)	27	56−87	21	98.6	1/3.7
-63	RaNi	NaOH (0.8)	30	92	15	93	1/6.1
-67	RaNi	NaOH (0.8)	50	90	20	90	1/5
-79	RaNi	NaOH (0.9)	20	90	4	83	1/6.6
				65	14		
-39	Rh/Al_2O_3	K_2CO_3 (1)	56	55	8	44	1/1
-40	Rh/Al_2O_3	NaOH (0.8)	50	58	72	>99	1/1.1
-48	Rh/Al_2O_3	aq HCl (1)	52	45	72	>99	2/1
-64	Rh/Al_2O_3	NaOH (1.0)	50	100	20	56	1/1.6
-50	Pt/C	NaOH (0.8)	50	28	48	40	1/3.2
				58	22		
-53	Pt/C	aq HCl (1)	50	52	5.5	87[c]	1/2.1
-55	Pt/C	NaOH (1.1)	50	28	48	14	1/3.2
				58	16		

[a] Note: All reactions were carried out in water. [b] Determined by NMR. [c] Large amount of impurities formed.

rings, Raney nickel would be most likely to afford product mixtures in which the thermodynamically favored isomer (i.e., 1,4-*trans*) would predominate.[10,11] Thus, a wide variety of conditions were screened to optimize the formation of the trans isomer using this catalyst as well as several others. Employing a standard loading of a 2:1 w/w ratio of catalyst and substrate, the following reaction parameters were studied: amount of base, nature of the base, temperature, time, and hydrogen pressure. The results are summarized in Table 1.

Since Raney nickel appeared to provide the best results in terms of conversion and trans/cis ratio, several different lots were selected for further study. The results are presented in Table 2.

Based upon this large number of experiments, the following information was obtained:

(1) The reaction temperature must be at least 50 °C to achieve >90% conversion.

(2) Sodium hydroxide (0.8−2.0 equiv based on **3**) gave the most consistent results in terms of the trans/cis ratio of **4**.

(3) The highest trans/cis ratios were obtained at higher temperatures and lower hydrogen pressures.[12]

(4) Although higher temperatures afforded higher trans/cis ratios, the lower hydrogen pressures used resulted in lower conversion of starting material (85% at 20 psi vs 95% at 50 psi).

(5) Higher temperatures caused some racemization to occur.

(6) The source of the Raney nickel affected both the % conversion as well as the trans/cis ratio.[13]

We found that trans/cis ratios as high as 7:1 could be obtained at temperatures between 70 and 90 °C and hydrogen pressures of 20−30 psi. However, it was also discovered that this ratio was dependent on the source of the Raney nickel catalyst. Different lots from the same supplier gave ratios that varied from 3.5:1 to 7:1. In fact, we observed that most of the catalyst types that gave the highest trans/cis ratios also gave the most variable results and the most racemization. After extensive testing of 10 different sample lots of catalyst from one supplier, a lot was chosen which gave a high trans/cis ratio with little or no racemization. However, when the full supply of catalyst was received and tested on a large scale, this same lot gave only a 3:1 trans/cis ratio of diastereoisomers and in addition caused extensive racemization (16% L-isomer detected by chiral HPLC). Therefore, a catalyst type was chosen which had given a lower ratio but had been the most consistent (3.5:1 trans/cis, 4−5% racemization).[14] This catalyst performed well on scale-up in the pilot plant, with the expected results being obtained in most cases.[15]

Although we were somewhat perplexed at first with regard to the cause of the racemization which occurred in two of the batches, we were able to explain these results once the conditions under which the racemization had occurred were examined. In these two pilot plant runs, the L-isomer content of **4** was 17.7% and 29.4%, respectively.

Upon examination of the conditions under which these two reductions were carried out, we found that, in both cases, the substrate was in contact with the catalyst for an extended period of time in the absence of a hydrogen atmosphere. This was due to some operational difficulties which had developed. Based upon these results, we felt that the high degree of racemization might be explained in the following manner.

In the first case (17.7% of the trans L-isomer), we learned that the catalyst and the compound **3** solution had been charged to the reactor but that the vessel was not pressurized with hydrogen for several hours. Since Raney nickel was present for an extended period without the hydrogen atmosphere (oxygen present), we believe that racemization occurred through the redox process shown below. The existence of this intermediate could lead to racemic product upon hydrogenation.[16]

Another piece of evidence supporting this hypothesis comes from the second case mentioned above wherein the isolated product was found to contain 29.4% of the undesired L-isomer. In this instance, the hydrogenator was filled up to

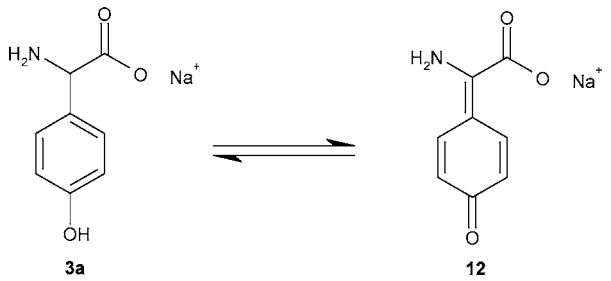
(10) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965.
(11) Rh/Al_2O_3 afforded 2:1 trans/cis mixtures under both acidic and basic conditions over a wide range of temperatures. Pt/C catalysis resulted in incomplete conversion as well as affording significant amounts of hydrogenolysis products (see ref 5). No reaction was observed with either Pd or Ru catalysts. The trans/cis ratios were monitored by NMR (see ref 6).
(12) The highest trans/cis ratio obtained was 7:1 (70 °C, 20−25 psi hydrogen, 22 h).
(13) The activity grade was equivalent to W-2.
(14) The presence of small amounts of the D-cis isomer ceased to be of concern when it was learned that this impurity could be removed in a later step (see text).
(15) A total of 15 hydrogenations were carried out with good consistency among 13 of these (see text).
(16) In all cases, less than 1% of the L-cis isomer was formed.

Table 2. **Step 3 → 4: screening of reaction conditions with Raney Nickel catalyst[a]**

ref	catalyst	temp (°C)	time (h)	unreduced (%)	4			
					R-trans	*S-trans*	*R-cis*	*S-cis*
19804-2	Aldrich	60	7	2.1	72.3	4.4	21.9	0.5
19807-2	PMC A-5000	60	8	2.4	72.7	5.5	21.2	0.6
19806-2	PMC A-5B00	60	11	1.2	72.7	9.3	17.2	0.9
19805-2	PMC A-5300	60	14	3.7	68.7	14.5	15.7	1.1
19808-2	PMC A-5300	60	21	2.4	70.9	9.9	18.4	0.9
19809-2	PMC A-5300	65	11	5.1	*b*			
19811-2	PMC A-5300 (different lot)	60	11		71.2	6.6	21.4	0.8

[a] Note: The trans/cis ratios were determined by NMR analysis of the solution from the reduction step (compound **3**). The analysis for enantiomeric purity was carried out on compound **4** using an HPLC method developed in our analytical group. All reactions were carried out using 1 equiv of sodium hydroxide and 40 psi of hydrogen. [b] The optical purity was not measured. The *trans*/*cis* ratio was 6.1/1 for compound **3**.

the full capacity of the vessel. Thus, there was little or no atmosphere of hydrogen above the level of the liquid, and agitation of the batch was poor. It was also observed that the rate of the reduction was considerably slower. These conditions would favor the redox equilibrium shown below with an intermediate quinine-methide **12**, with the result being racemization. Subsequently, the process conditions



3a **12**

were modified in that the reaction temperature was lowered slightly and full hydrogen pressure was applied rapidly after charging and maintained throughout the reaction. The last five batches prepared under these conditions all contained less than 5% of the L-isomer (combined cis and trans).

In an effort to further substantiate the oxidative racemization hypothesis, samples of D-4-hydroxyphenylglycine and D-phenylglycine were subjected to the identical reaction conditions in the absence of hydrogen. It was assumed that if the mechanism for the racemization involved the quinone-methide-like structure **12**, then no racemization would occur with the D-phenylglycine.

In the event, it was found that *both* substrates underwent a small degree of racemization (2−5%) when exposed to aqueous sodium hydroxide and Raney nickel in the absence of hydrogen. Thus, the explanation for this phenomenon is still unclear at this time. However, the possibility cannot be ruled out that two different mechanisms are operating here.

It was found that the course of the reaction could be followed most easily using NMR. One could see the disappearance of the aromatic protons as the reduction progressed and, at the same time, view the appearance of the methine proton on the cylcohexyl carbon bonded to the hydroxyl group. Fortunately, the chemical shifts for this proton in the cis and trans isomers were different enough that one could obtain a rather accurate isomer ratio based on the integration. However, in the long run, a more quantitative method (e.g., HPLC) will be required.

Initially, it was decided that it would be advantageous to isolate **4** as a solid intermediate for the purposes of purification. In addition, we hoped that further enrichment of the trans/cis mixture could be effected at the same time. Thus, an aqueous solution containing **4** was acidified under a variety of conditions, and the amino acid products were analyzed by HPLC for content. Acidification of an aqueous solution of the sodium salt **4** with 0.1 N HCl (0.43 equiv based on theory) afforded the corresponding acid in an overall yield of 33% with a trans/cis ratio of 18/1.

At this point, we decided to investigate this reaction further and to determine more precisely the composition of the hydrogenation mixture. Thus, a sample of the hydrogenation solution (after filtration of the catalyst) was analyzed by LC/MS. The results are represented in Figure 1 with tentative structures assigned based upon the observed molecular weights (note: these impurities account for 10−15% of the total mixture).

With the formation of such a multitude of products, we decided that perhaps the most expeditious course would be to react the sodium salt **4** with the sulfonyl chloride **2** and isolate the sulfonamide **5**, which could be purified further if necessary. The reaction was carried out in the presence of acetonitrile and triethylamine at 0 °C, and the product **5** was isolated in an overall yield of 60% (based on **3**) with the following results:

(i) 98.4% purity by HPLC area normalization (cis and trans);

(ii) 3.8/1 trans/cis ratio (D-isomers);

(iii) 3.4% trans L-isomer;

(iv) 0.5% cis L-isomer.

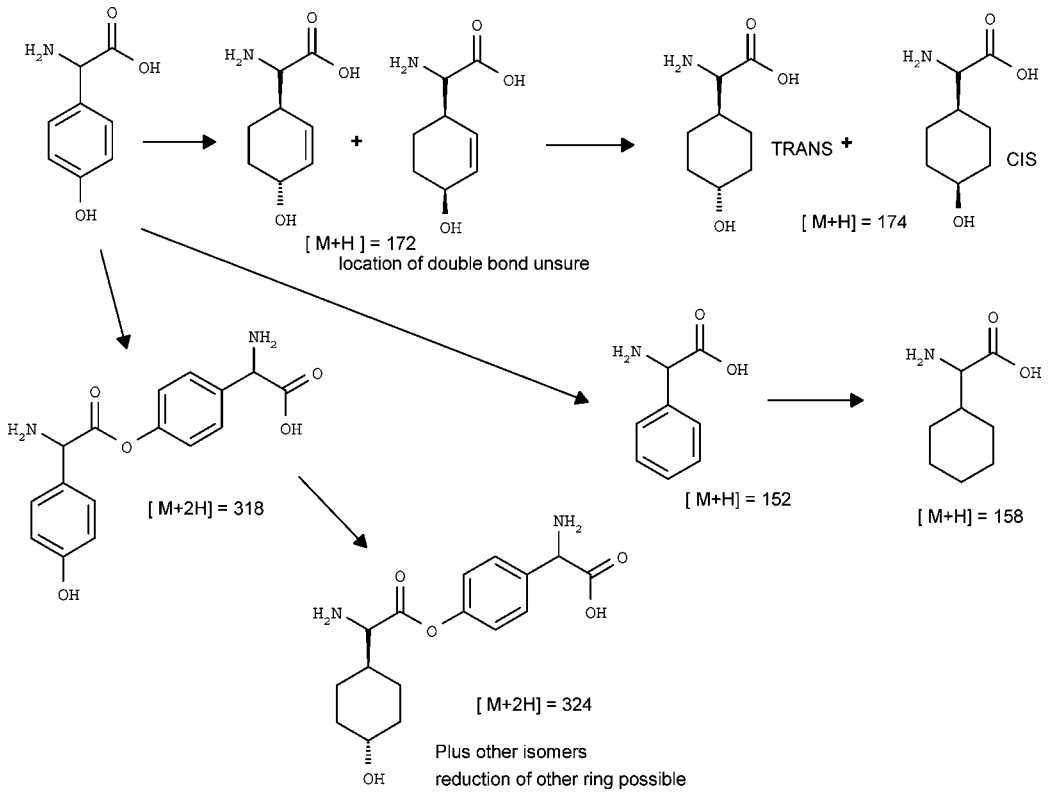
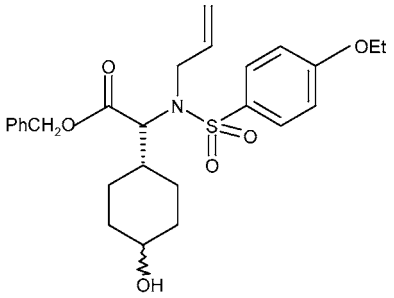


Figure 1.

We found that this mixture was suitable for use in the subsequent steps, and therefore, no further purification of this compound was effected.

Phenylmethyl *trans*-α-[*N*-(4-Ethoxyphenylsulfonyl)-amino]-4-propoxycyclohexaneacetate (8). As mentioned in the Introduction, the formation of the *n*-propyl ether was the most problematic aspect of the synthesis. Not only was the compound a secondary alcohol but also, in addition, there were base sensitive functionalities present in the molecule, such as the α-amino ester. Using typical Williamson ether synthesis[17] conditions (e.g., NaH, *n*-propyl bromide, or allyl bromide) lead only to complex mixtures. The palladium catalyzed reaction of **6** with diallyl carbonate[18] afforded the N-allylated compound **13** as the sole product.



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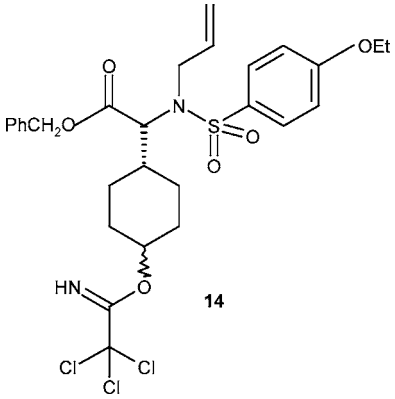
Reacting **6** with allyl 2,2,2-trichloroacetimidate under Lewis acid catalyzed conditions[19] gave the trichloroacetimidate **14** of the alcohol **13** as the only product. At the time



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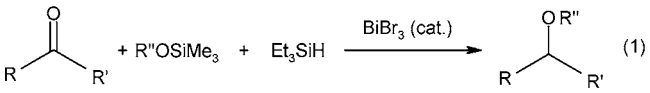
this work was in progress, a publication appeared in which it was shown that the reductive heterocoupling of a carbonyl compound with an alkoxy silane could be smoothly effected with triethylsilane in the presence of bismuth bromide (eq 1).[20]



This approach appeared to be applicable to our situation. The TMS ether of compound **6** was prepared and reacted with propionaldehyde and triethylsilane in the presence of a catalytic amount of bismuth bromide under conditions similar to those described by Komatsu.[20] We were gratified to find that the desired ether **8** was formed in 70% yield along with

(17) For a review, see: Feuer, H.; Hong, J. *The Chemistry of the Ether Linkage*; John Wiley & Sons: New York, 1969; pp 446, 460.
(18) Lakhmiri, R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1989**, *30*, 4669.
(19) Wessel, H.-P.; Iverson, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.
(20) Komatsu, N.; Ishida, J.; Suzuki, H. *Tetrahedron Lett.* **1997**, *38*, 7219.

15% of alcohol **6**. The starting alcohol was the result of hydrolysis of the TMS ether due to the presence of trace amounts of water in the acetonitrile.[21] The use of the more stable TBDMS ether **6a** afforded the *n*-propyl ether **8** in 88% yield. The generality of this approach to ether formation was investigated further with the following observations and conclusions.[22]

Over the course of the reaction, a gray solid precipitate formed. By elemental analysis this was shown to be bismuth metal. In a separate experiment, it was demonstrated that the catalytic activity resided with the filtrate and not with the metal. When the interaction of triethylsilane and bismuth bromide was monitored by NMR, it was found that the signal at δ 0.61 ppm for the methylene protons in the triethylsilane changed from a multiplet to a simple quartet upon addition of bismuth bromide. Furthermore, the multiplet for the −Si*H* at δ 3.60 ppm disappeared while a new signal appeared at δ 10.36 ppm. All of these results are consistent with the formation of hydrogen bromide, bismuth metal, and triethylsilyl bromide as the products of this reaction. The hydrogen bromide goes on to react with the acetonitrile to form acetimidoyl bromide.[23] This adduct was ineffective in catalyzing O-alkylations. On the other hand, commercial triethylsilyl bromide when used in catalytic amounts together with triethylsilane worked as effectively as the $BiBr_3/Et_3$-SiH combination in the reductive etherification of a variety of silyl ethers.[22] This served further to confirm our conclusion, based on the NMR experiment, that the triethylsilyl bromide formed in situ from $BiBr_3/Et_3SiH$ is the actual catalyst in the reaction. For our scale-up work, we found it more convenient to use the $BiBr_3/Et_3SiH$ combination to generate the triethylsilyl bromide due to the difficulties in handling the latter (hygroscopicity).

One unexpected benefit of using the TBDMS ether **6a** was that it allowed for the virtually complete removal of the undesired cis isomer. Thus, the reaction was carried out using TBDMSCl and imidazole in DMF followed by an aqueous workup and extraction of the product into methyl *tert*-butyl ether. The desired product **6a** was crystallized by the addition of heptane to the partially concentrated solution (the pure cis isomer was isolated from the mother liquors by chromatography and was found to be an oil). Starting with a 3.5/1 trans/cis mixture of **6**, **6a** was isolated in 68% yield (87% efficiency based on the amount of trans isomer present in **6**) and then with a 121/1 trans/cis ratio based upon the HPLC and NMR analysis. At this point, the enantiomeric purity (D-**6a**, trans + cis) was 96%.

For the scale-up of the succeeding step (formation of the *n*-propyl ether **8**), there were two issues which needed to be addressed. These were the exothermic nature of the reaction and the water content of the starting materials. On a small scale, the catalyst (bismuth bromide) was added to the reaction mixture last. Under these conditions, an induction period was observed followed by a rise in the temperature of the mixture. To maintain better control, we decided to add the propionaldehyde to the mixture of the TBDMS ether, triethylsilane, and bismuth bromide in the acetonitrile. By monitoring the rate of addition, the exothermic nature of the reaction could be controlled.[24]

Based on the experience from several experiments, we learned that the water content of the solvent (acetonitrile) and the reagents had a significant influence on the yield of the reaction, due to the hydrolysis of the TBDMS ether in the presence of water and bismuth bromide. Extra precautions were taken to ensure the anhydrous nature of the reaction. Thus, using the conditions mentioned above, the product **8** was isolated after an aqueous workup by precipitation from ethyl acetate/heptane in 85% yield and greater than 99% purity (HPLC, area normalization). The product was found to contain 0.24% of the L-*trans*-isomer of **8**, and less than 0.5% of the D-*cis*-isomer.

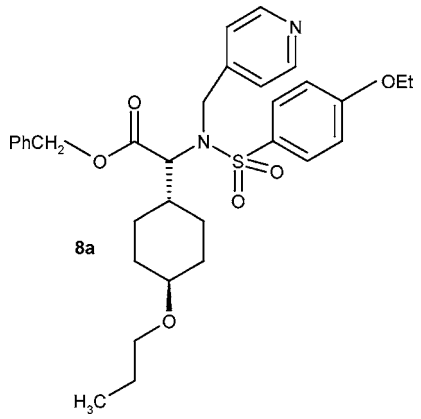
Phenylmethyl *trans*-*R*-[[*N*-(4-Ethoxyphenylsulfonyl)-*N*-(4-pyridinylmethyl)]amino]-4-propoxy-cyclohexaneacetate (8a). In addition to the procedure used in the Research synthesis, two other sets of reaction conditions were investigated, i.e., potassium *t*-amylate in toluene, sodium hydride in THF. However, neither of these provided useful amounts of product. Thus, it was decided to optimize the potassium carbonate/DMF process for scale-up.

The main issues which needed to be addressed were the following:

(i) since the yield was low, optimization studies were needed in order to increase the conversion in the alkylation step and to improve the workup to provide for a better fit in the pilot plant (reaction time, concentration, stoichiometry, etc.);

(ii) it appeared that the alkylation product (**8a**) was not a solid, nor was the HCl salt (isolation issues);

(iii) if **8a** could not be isolated, a workup procedure would be needed in order to ensure that the crude compound would undergo the debenzylation successfully and that **9** could be isolated and purified further, if necessary.



Fortunately, we were able to begin our efforts starting from the procedure which had been used for the first scale-up in the kilo lab. This involved the use of potassium

(21) Alkyl TBDMS ethers can be hydrolyzed in wet acetonitrile in the presence of a catalytic amount of bismuth bromide: Bajwa, J. S.; Vivelo, J.; Slade, J.; Repič, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021.

(22) Bajwa, J. S.; Jiang, X.; Slade, J.; Prasad, K.; Repič, O.; Blacklock, T. *Tetrahedron Lett.* **2002**, *43*, 6709.

(23) Janz, G. L.; Danyluk, S. S. *J. Am. Chem. Soc.* **1959**, *81*, 3850.

(24) As measured in an RC-1 calorimeter, the adiabatic temperature rise was 18 °C.

Table 3. **Step 8 → 8a: optimization experiments**[a]

ref	mL of DMF/ g of **8**	time (h)	extract. solvent	yield[b] (%)	HPLC[c] (%)			
					8a	*cis*-**8a**	**8**	Sol
-106	10/1	16	EtOAc	87	93.2	0.9	5.9	trace
-112	10/1	42	toluene	85	92.2	0.9	0	6.9
-115	2.6/1	68	toluene	80	98.8	1.2	0	trace
-124c	2.1/1	22	toluene	89	95.5	1.0	0	3.5

[a] Note: All reactions were conducted at room temperature using the stoichiometry described above. [b] Corrected for solvent content. [c] Percentages based on area normalization.

carbonate along with a catalytic amount of TDA-1.[25] It had been found that, without the TDA-1, the reaction was considerably slower and that 1−2% racemization occurred. Under these conditions, the reaction time was reduced by 50% and the amount of racemization was <0.3%. One other problem identified at this time involved the presence of an impurity in the crude product which acted as a powerful catalyst poison in the next step. This was believed to be picolyl chloride or a homopolymer which was derived from the excess picolyl chloride hydrochloride after neutralization. The use of an acidic workup did not completely eliminate this impurity.

Initially, the reaction was carried out in the following manner: compound **8**, picolyl chloride hydrochloride (1.5 equiv), powdered potassium carbonate (10 equiv), and TDA-1 (10 mol %) were stirred in DMF at room temperature overnight. The workup involved filtration to remove the solids and addition to 10% aqueous citric acid followed by extraction into ethyl acetate. The extracts were washed with 6 N HCl (to remove the some of the excess picolyl chloride, DMF, and TDA-1) and water. Under these conditions, approximately 6% of **8** was present in the crude product. It is interesting to note that, based on an HPLC analysis of the acid washes, none of the product **8a** was extracted despite the fact that a basic pyridine ring was present in the molecule.

This procedure was used as the basis for the following investigation. The results are summarized in Table 3.

In experiment -106, the ethyl acetate solution was washed with water until the washes were neutral to pH paper. That the reaction was incomplete and a large volume of waste was generated were the main concerns. In experiment -112, the reaction time was extended to ensure complete conversion of **8**. Monitoring was done by HPLC. Toluene was used as the extraction solvent since ethyl acetate had given poor phase separations. An alumina treatment was added to remove colored polar impurities. One other benefit of using toluene was that less water washes were required. To further improve the throughput, experiment -115 was carried out at about 4 times the concentration. This helped further reduce the volume of waste generated. Extending the reaction time from 42 to 68 h did not have a significant effect on the yield or purity of **8a**. Increasing the concentration further (experiment −124c) and frequent monitoring indicated that the reaction was actually complete in only 22 h.

(25) Tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) has been shown to be a good solid−liquid-phase transfer catalyst: Soula, J. *J. Org. Chem.* **1985**, *50*, 3717.

Table 4. **Step 8a → 9: initial optimization experiments**

ref	solvent	time (h)	yield (%)	HPLC (%)	recryst. solv.	recovery	HPLC (%)
-121	HOAc	16	45	86.8	2-propanol	56	96.7
-128	EtOAc	16			MeOH	55	>99
-133	HOAc	3	80	98.0	MeOH	72	>99

The final series of experiments included the following:

(i) The maximum reaction volume was further reduced by using the extraction solvent (toluene) rather than DMF to wash the potassium carbonate filter cake. This allowed for a proportional reduction in the amounts of citric acid and toluene. Overall, these changes reduced the maximum volume by 50%.

(ii) The slow filtration to remove the potassium carbonate was improved by adding Celite to the reaction mixture.

Initially, we had planned to crystallize the benzyl ester **8a** as either the free base or the HCl salt. Thus, a sample was purified by preparative HPLC to provide seed crystals for the crystallization. However, even using seeding techniques, the free base could not be crystallized probably due to its high solubility in all the solvents tested with the exception of water and heptane. In addition, it proved to be extremely difficult to crystallize the HCl salt, even starting with a sample of the free base that had been purified by chromatography. The best that could be obtained was a solidified foam. Attempts at preparing other salts were equally unsuccessful.

***trans*-*R*-[[*N*-(4-Ethoxyphenylsulfonyl)-*N*-(4-pyridinylmethyl)]amino]-4-propoxycyclohexaneacetic Acid (9).** Since the isolation of the alkylated sulfonamide (**8a**) proved to be difficult, it was decided to convert it directly to the carboxylic acid by palladium-catalyzed hydrogenolysis. Initially, the following conditions were employed. The toluene solution of the **8a** was filtered through alumina to remove polar impurities and to dry the solution. Next, the solvent was exchanged for acetic acid (final ratio = 10:1 mL/g **8a**). Acetic acid was used because we had observed that compound **9** was not soluble in most organic solvents and would precipitate during the hydrogenolysis, making it difficult to separate from the catalyst. The hydrogenolysis was carried out at 50 psi using 10% Pd/C, 50% water wet (a 10% loading based on the theoretical amount of **8a** present was used). The reaction was monitored by HPLC and was found to be complete in 1−3 h. The product **9** was isolated by filtration, concentration of the solution, and addition of water. The crude product was then recrystallized. With this as a starting point, a series of experiments was carried out in order to further define the reaction conditions as well as the crystallization and recrystallization procedures. The results are summarized in Table 4.

For the first experiment in the table, isolated **8a** (gummy solid) was used in order to become familiar with the process. The product was isolated by concentrating the solution (after filtration of the catalyst) and triturating with water. In one instance we attempted to hydrogenolyze the ethyl acetate solution of **8a** as it was obtained from the previous reaction (experiment -128). Due to the insolubility of **9** in ethyl

Table 5. **Step 8a → 9: further optimization experiments**

ref	objective	yield[a] (%)	HPLC (%)	Pd (ppm)
-162	improve filterability of **9**	80	98.3	71
-176	scale-up using catalyst from pilot plant	74	98.7	26
-189	reduce Pd levels	75	>99	20

[a] Yields are calculated based on **8**.

acetate, the isolation was extremely difficult. However, it was possible to recrystallize the crude product to high purity. Obviously, neither of these procedures could be scaled up. Thus, in the third experiment (-133), acetic acid was used and the reaction was monitored carefully for completeness. After 3 h, the catalyst was removed, and the solution was concentrated to approximately 20% of the initial volume and then added carefully to water with seeding. This afforded a good yield of the desired product which after recrystallization gave **9** in high purity.

One other major concern with the hydrogenolysis step was the concomitant reduction of the pyridine ring. Depending on the conditions used, a significant amount of the piperidine analogue was formed.[26] Fortunately, the rate of debenzylation was quite a bit faster than the rate of ring reduction.[27] In a control experiment, compound **9** was subjected to the conditions of the hydrogenolysis for 72 h. Analysis of the reaction mixture by HPLC indicated that about 75% of the starting material had been converted to the overreduced side product at this point (an authentic sample was prepared for comparison). Therefore, the reaction was carefully monitored for the disappearance of the starting material. This served to preclude the formation of the overreduced side product.

With these results in hand, we next sought to further optimize the reaction conditions in preparation for scale-up. Specifically, the following items were addressed:

(i) demonstrate that the solvent exchange from toluene (**8a**) to acetic acid is feasible with regard to the stability of the compound and ease of operation;

(ii) further develop the isolation of crude **9** (addition of the acetic acid solution to water gave a solid which was very slow to filter);

(iii) control the amount of palladium in **9** (up to 500 ppm of palladium was present due to breakthrough during the filtration stage);

(iv) further refine the conditions for the recrystallization.

Several experiments were carried out in order to address these issues, and the results are summarized in Table 5.

That the solvent exchange from toluene to acetic acid by replacement distillation was feasible was demonstrated in all three of the experiments listed in the table as this was done in each case. In addition to the results obtained, a study was carried out in which **9** was held as an acetic acid solution for 12 days with monitoring by HPLC at periodic intervals. This was done to further confirm the stability of the product in acetic acid since it was our intention to accumulate the solution from several batches and combine them for the crystallization.

As was mentioned previously, the filtration of the acetic acid solution of **9** was problematic due to the poor physical characteristics of the solid. The filterability was greatly improved by pouring the concentrated acetic acid solution into a dilute aqueous solution of sodium chloride. The product obtained was granular in nature and easily filtered (experiment -162). Experiment -176 involved a use test of the actual lot of catalyst we intended to employ and also provided us with an opportunity to scale-up the reaction in the laboratory prior to implementation in the pilot plant.

Although **9** was not the final drug substance, it was decided to control the palladium content at this point since we wished to avoid extensive purification in the last step, if possible. To ensure low palladium content (<2 ppm in the final drug substance), the following strategy was adopted. Filter aid was added before the catalyst filtration, the suspension was filtered through a wet-packed pad of filter aid, and the isolated product was further purified by recrystallization which included an adsorbent.

A series of experiments was carried out in which different recrystallization solvents as well as different adsorbents were used in order to effect the final purification and remove the last traces of palladium. The results are summarized in Table 6.

Based on these results, it was decided to use methanol and the carbon PICA1400 (experiment -31) since the recovery was reasonably good and the palladium content was within acceptable limits. Thus, the optimized process involved dissolving the substrate in methanol (25 mL/g) containing 10% of PICA1400 at reflux. The suspension was filtered while hot, and the filtrate concentrated to approximately 50% of the original volume at which point **9** began to crystallize. When this purification method was scaled up in the laboratory (150 g), the same results were obtained except that the recovery was better (88%) due to a longer hold time during the crystallization.

***trans*-*R*-[[*N*-(4-Ethoxyphenylsulfonyl)-*N*-(4-pyridinylmethyl)]amino]-*N*-hydroxy-4-propoxy-cyclohexaneacetamide Hydrochloride (10, MMP090).** With an efficient synthesis of **9** in hand, all that was needed to complete the synthesis was to form the hydroxamic acid. Most importantly, we needed to carry out this transformation in such a way as to prevent epimerization at the chiral center. It was felt that the best way to accomplish this would be to carry out the reaction under Schotten−Baumann conditions.[28] Thus, the acid chloride was prepared by the addition of oxalyl chloride to a slurry of **9** and a catalytic amount of DMF in THF at 0 °C. The reaction mixture was held for 1 h at this temperature and then added to a solution of hydroxylamine in THF/water[29] at −10 °C. After 2 h at 0−5 °C, the THF and water were removed by distillation and replaced by ethyl acetate.

(26) The compound was identified by comparison with an authentic sample prepared independently.

(27) A reaction carried out for 72 h afforded a mixture containing 75% of the over-reduced product and only 25% of **9**.

(28) For an alternative procedure, see: Ando, W.; Tsumaki, H. *Synth. Commun.* **1983**, 1053.

(29) The hydroxylamine was purchased as a 50% aqueous solution.

Table 6. **Step 8a → 9: recrystallization of compound 9[a]**

ref	-21	-30	-39	-27	-29	-31	-33	-35	-37
solvent adsorbent	EtOAc/CH_3CN none	CH_3CN/MeOH carbon PICA P1400	*n*-BuOAc/*i*PrOH carbon PICA P1400	MeOH chelating resin SIR-400	MeOH chelating resin SIR-300	MeOH carbon PICA P1400	MeOH carbon PICA GX213	MeOH neutral alumina	MeOH none
recovery (%)	86	75	62	75	59	75	75	75	83
HPLC[b] (%)	>99	>99	>99	>99	>99	>99	>99	>99	>99
Pd (ppm)	15	<2	<2	4	39	<2	7	27	30

[a] Note: All reactions were carried out on a 1 g scale. [b] Area normalization.

Table 7. **Step 9 → 10: reaction conditions**

ref	$(COCl)_2$[a] (equiv)	H_2NHOH[a] (equiv)	HPLC (%) **10**	HPLC (%) **9**	yield[b] (%)
96-2	1.5	10	96.1	2.5	78
108-1	1.25	10	98.3	1.0	98
109-2	1.25	10	94.5	2.7	78
113-4	1.5	20	97.3	1.5	90
115-4	1.25	20	95.9	1.8	92
119-7	1.25	20	97.5	0.3[c]	56[d]

[a] Based on the amount of **9** used. [b] The product was obtained as a gummy solid or foam after solvent removal. [c] The ethyl acetate solution of **10** was washed with an aqueous Borax solution. [d] Overall yield from **9** after crystallization (see below).

Table 8. **Step 9 → 10: isolation**

ref	solvent (ratio)	HPLC (%) **10**	HPLC (%) **8**	yield[a] (%)
111-1	EtOH/MTBE (1:2)	97.2	1.7	66
114-1	EtOAc/EtOH/MTBE (1/1.6/3.2)	98.2	1.1	87
115-4	EtOAc/EtOH/MTBE (1/1.1/2.3)	98.2	1.4	90
118-1	EtOH/EtOAc (1/5.7)	97.1	1.9	88

[a] Refers to the yield from crude to crystallized **10**.

From our initial work, it appeared that the yield was mainly dependent upon the quantities of oxalyl chloride and hydroxylamine used. Therefore, these two parameters were studied further. The results are summarized in Table 7.

Although 10 equiv of aq. hydroxylamine appeared to afford a high conversion in one of the experiments (108-1), it was decided to develop the process using 20 equiv and add a Borax wash in order to ensure a low level of **9** in the drug substance since this impurity was found to be difficult to remove (experiment 119-7).

Since it proved rather difficult to crystallize the crude product, the compound was converted to the HCl salt. This was easily accomplished by the addition of ethanolic HCl to a solution of the free base. The basic procedure involved dissolving crude **10** in a suitable solvent or solvent mixture and adding an antisolvent (50% of the total amount to be used). This was followed by the addition of ethanolic HCl (60% of the total amount needed). After seeding, the remaining antisolvent and acid were added. Although antisolvent and the HCl could be added all at once, this procedure afforded crystalline **10** with the highest purity and the best reproducibility. A variety of solvent mixtures were investigated, and the results are summarized in Table 8.

Since no definitive advantage was gained by using the three-solvent mixture, it was decided in the interest of simplicity to use the ethanol/ethyl acetate mixture (experiment 118-1). The procedure scaled up well in the pilot plant where a 74% overall yield from **9** was obtained.

Although the purity of the drug substance at this point was acceptable, it became necessary to perform a recrystallization in order to obtain the desired polymorph. During the course of this work, several different polymorphic forms had been identified; however, only one was considered stable enough for further development. The final conversion was carried out in a mixture of ethanol/*tert*-butyl methyl ether (the solution was seeded with the correct polymorph to ensure reproducibility) and afforded a 92% recovery of the desired form with greater than 99 wt % chemical purity and 99.9% optical purity.

In summary, a highly efficient 9-step synthesis of the dual matrix metalloprotease/tumor necrosis factor MMP090 was developed and demonstrated on a kilogram scale in 11% overall yield starting from D-phenylglycine. The most important features of the chemistry are the following: (1) the use of Raney nickel to effect the reduction of the aromatic ring of D-phenylglycine **3** to afford predominantly the *trans*-cyclohexanol without racemization; (2) the highly efficient fractional crystallization of *trans*-**6a** to remove the undesired cis isomer; (3) the bismuth bromide catalyzed reductive coupling of TBDMS ether **6a** with propionaldehyde to give the *n*-propyl ether **8** in good yield and purity; (4) the selective hydrogenolysis of the benzyl ester without reduction of the pyridine ring; and finally (4) hydroxamic acid formation under mild conditions without racemization.

Experimental Section

General. Melting points were determined on a Thomas–Hoover melting point apparatus and were uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (^{1}H NMR at 300 MHz). Analytical high performance liquid chromatography (HPLC) was carried out using a Waters Alliance 2690 Separations Module, a Waters 996 Photodiode Array Detector (MaxPlot), and the following columns: 4.6 mm × 25 cm Inertsil 5 μ ODS-2 (MetaChem) and 4.6 × 15 cm Nucleosil 3 μ C18 (MetaChem). Reactions were carried out under an atmosphere of nitrogen. Residual water content was determined by Karl Fischer titration. The Raney nickel catalyst (Grade A-5300) was purchased from Activated Metals and Chemicals, Inc, Sevierville, TN.

4-Ethoxybenzenesulfonyl Chloride 2. Into a 12-L four-necked round-bottomed flask equipped with a mechanical

stirrer, condenser, nitrogen inlet, addition funnel, heating unit, and thermometer probe were charged 4-hydroxybenzenesulfonic acid sodium salt dehydrate (2.0 kg, 8.62 mol), water (1.7 L), and 15% sodium hydroxide solution (3.8 kg). The solution was warmed to 35 °C, and diethyl sulfate (1.76 kg, 11.46 mol) was added over 10 min. The solution was heated at an internal temperature of 95−100 °C and held for 16 h. The reaction mixture was cooled to 23 °C over 2.5 h and held at this temperature for an additional 1 h. The solid product was collected by filtration, and the filter cake was washed with acetone (2 × 750 mL). After drying under vacuum at 45 °C, 1766 g (87% corrected yield) of 4-ethoxybenzenesulfonic acid sodium salt was obtained as an off-white solid: Karl Fischer 4.3% water; ^{1}H NMR (CD_3OD) δ 7.75 (d, J = 9.4 Hz, 2H), 6.94 (d, J = 9.4 Hz, 2H), 4.05 (q, J = 7.5 Hz, 2H), 1.38 (t, J = 7.5 Hz, 3H). This compound was used in the following step without further purification.

Into a 12-L four-necked round-bottomed flask equipped with a mechanical stirrer, nitrogen inlet, addition funnel, thermometer, and a condenser set for downward distillation were placed 4-ethoxybenzenesulfonic acid sodium salt (1.2 kg, 5.3 mol), toluene (6 L), and DMF (77.5 g). The heterogeneous reaction mixture was heated to a 115 °C jacket temperature, and the toluene/water mixture was removed by azeotropic distillation (600−700 mL). Once the distillation was completed, the batch temperature was reduced to 80 °C, and thionyl chloride (1.9 kg, 16 mol) was added over 5.5 h while maintaining an internal temperature of 75 °C. Upon completion of the addition, the mixture was held for an additional 5 h at 80 °C, cooled to room temperature, and held for 16 h. The reaction mixture was heated at an internal temperature of 45−50 °C under reduced pressure (95−100 mmHg), and toluene and excess thionyl chloride (approximately 3 L) were removed by distillation. After cooling to room temperature, the concentrate was filtered and the filter cake was washed with toluene (300 mL). The filtrate was further concentrated by distillation (45−65 °C, 95−100 mmHg) to afford 4-ethoxybenzenesulfonyl chloride (1.18 kg) as an orange liquid. The product was found to contain toluene (27%) and DMF (<1%) by NMR analysis resulting in a corrected yield of 863.3 g (74%): ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 10.0 Hz, 2H), 6.94 (d, J = 10.0 Hz, 2H), 4.07 (q, J = 6.9 Hz, 2H), 1.38 (t, J = 6.9 Hz, 3H). This mixture was used in the following step without further purification.

(*R*)-α-[*N*-[(4-Ethoxyphenyl)sulfonyl]amino]-4-hydroxycyclohexanacetic Acid 5. Into an RC1 Mettler Toledo Reactor Calorimeter fitted with a 1-L MP 10 glass reactor were added deionized water (300 g) and sodium hydroxide (12 g, 0.3 mol). To the stirred solution was added d-(−)-(4-hydroxyphenyl)glycine **3** (50.2 g, 0.3 mol), and the mixture was stirred at 30 °C for 15 min to dissolve the solids. The solution was treated with Raney nickel catalyst (250 g), and the reactor was purged with nitrogen 3 times and hydrogen 3 times. The reactor was pressurized to 30 psi with hydrogen and heated to 62 °C over 20−30 min and held at this temperature for 15 h with stirring. After cooling to room temperature and purging of the vessel with nitrogen, the suspension was filtered through a pressure filter equipped with a cellulose acetate filter pad (pore size 0.8 μ, 142 mm diameter) under 30 psi of nitrogen. At the completion of the filtration, the filter cake was washed with deionized water (200 mL), and the filtrates were combined. A portion of this solution containing **4** was concentrated, and the residue was analyzed by NMR to determine the trans/cis ratio (5.3:1) and the extent of conversion (96.6%).[30] The solution of **4** (1 kg, 0.36 mol based on **3**) was placed in a 3-L four-necked round-bottomed flask equipped with a mechanical stirrer, condenser, nitrogen inlet, addition funnel, and thermometer probe, and acetonitrile (660 mL) was added. The solution was cooled to 0 °C, and triethylamine (73.3 g, 0.72 mol) was added followed by compound **2** (104 g, 0.47 mol), which was added dropwise over 1.5 h while maintaining the temperature at 0 °C. The reaction mixture was held at this temperature for an additional 2 h, allowed to warm slowly to room temperature over 1 h, and held at this temperature for an additional 2 h. The acetonitrile and excess triethylamine were removed by distillation in vacuo to reduce the volume of the batch by 50%. The pH of the solution was adjusted to 7.7−8.5 with 1 N sodium hydroxide, and the solids were removed by suction filtration. The solids were washed with water (100 mL), and the combined filtrate and wash were extracted with ethyl acetate (300 mL). The aqueous portion was treated with 2 N HCl (4.5 mL, 9 mmol) and ethyl acetate (300 mL). After stirring for 15 min, the organic layer was discarded, and the pH of the aqueous portion was adjusted to 2.0 with 2 N HCl (125 mL added slowly over a 1 h period). The resulting solids were collected by suction filtration, washed with water (600 mL), and dried in vacuo at 70 °C for 16 h to give 77.1 g (59%, based on **3**) of **5** as an off-white solid (4/1 trans/cis mixture): mp 80−83 °C; ^{1}H NMR (D_2O−NaOD) δ 7.58 (2H, d, J = 8.9 Hz), 6.91 (2H, d, J = 8.9 Hz), 4.06 (2H, q, J = 7.0 Hz), 3.38 (1H, m), 2.87 (1H, d, J = 7.9 Hz), 1.85−1.65 (3H, m), 1.39−1.15 (5H, m), 1.02 (2H, m), 0.89 (1H, m), 0.65 (1H, m). Anal. Calcd for $C_{16}H_{23}NO_6S\cdot H_2O$: C, 51.19; H, 6.71; N, 3.73. Found: C, 51.31; H, 6.85; N, 3.66.

Phenylmethyl (*R*)-α-[*N*-(4-Ethoxyphenylsulfonyl)amino]-4-hydroxycyclohexaneacetate 6. Into a 4-L four-necked round-bottomed flask equipped with a mechanical stirrer, condenser, nitrogen inlet, addition funnel, and thermometer probe were placed **5** (50.0 g, 0.137 mol) and DMF (500 mL). To the solution was added dicyclohexylamine (32.6 g, 0.178 mol) at such a rate that the temperature was maintained below 25 °C. Benzyl bromide (31.1 g, 0.178 mol) was introduced while again maintaining the temperature below 25 °C during the addition. The reaction mixture was stirred at ambient temperature for 5 h. The resulting solids were filtered with suction, and the filter cake was washed with DMF (50 mL). A 2-L four-necked round-bottomed flask equipped with a mechanical stirrer, nitrogen inlet, and addition funnel was charged with water (1755 mL), sodium chloride (35.1 g), and *n*-heptane (206 mL), and the mixture was stirred for 5

(30) The trans/cis ratio was determined by comparing the integrated peak areas at 3.99 ppm (cis) and 3.56 ppm (trans): ^{1}H NMR (270 MHz, D_2O) δ 3.99 (m, part of 1H), 3.56 (m, part of 1H), 3.05 (d, J = 6.0 Hz, 1H), 2.0−0.9 (m, 9H). Aromatic protons for the unreduced amino acid: 7.02 (d, J = 8.2 Hz, 2H), 6.61 (d, J = 8.2 Hz, 2H). The percent conversion was calculated from the following equation: conversion % = [1 − A/2 ÷ A/2 + B] × 100. A = the total area of the olefin/aromatic hydrogens at 6−8 ppm. B = area of the peak at 3.05 ppm.

min. The solution of the filtrate from above was added to the water/heptane solution over 30 min. The resulting slurry was stirred for an additional 30 min and then filtered using suction. The solid was washed with water (800 mL) and dried at 60−65 °C under reduced pressure to give 62.0 g (93%, corrected) of **6** as a 3.8/1 mixture of trans/cis isomers: mp 113−116 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 and 6.87 (d of d, J = 8.3 Hz, 4H), 7.15 (m, 5H), 5.12 (m, 1H), 4.88 (s, 2H), 4.04 (q, J = 6.60 Hz, 2H), 3.75 (m, 1H), 3.49 (m, 1H), 1.94 (m, 2H), 1.44 (t, J = 6.60 Hz, 3H), 1.14−1.59 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.6, 162.8, 135.1, 131.1, 129.8, 129.0, 128.7, 115.0, 70.5, 67.7, 66.1, 64.3, 60.3, 40.8, 40.5, 35.1, 35.0, 32.3, 27.7, 26.9, 26.7, 26.1, 23.4, 22.2, 15.0; MS m/z 448 (M^+). Anal. Calcd for $C_{23}H_{29}NO_6S$: C, 61.72; H, 6.53; N, 3.13. Found: C, 61.94; H, 6.68; N, 3.09.

Phenylmethyl *trans*-4[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-[*N*-(ethyloxyphenylsulfonyl)-amino]cyclohexaneacetate 6a. Into a 1-L three-necked round-bottomed flask equipped with a mechanical stirrer, thermometer, nitrogen inlet, and addition funnel were charged **6** (53.0 g, 0.116 mol) and DMF (400 mL). Imidazole (11.9 g, 0.174 mol) was introduced followed by a solution of *tert*-butyldimethylsilyl chloride (23.6 g, 0.150 mol) in DMF (100 mL) (the solution of *tert*-butyldimethylsilyl chloride in DMF was prepared by warming to 35 °C followed by cooling to 20 °C prior to addition), which was added over a 10 min period. The reaction mixture was stirred for 4 h at room temperature and then diluted with methyl *tert*-butyl ether (MTBE, 500 mL) and water (600 mL). The layers were separated, and the aqueous layer was extracted with MTBE (500 mL). The organic layers were combined, washed with water (2 × 500 mL), and filtered through Celite. The cake was washed with MTBE (100 mL), which was combined with the filtrate. The solution was concentrated under reduced pressure to a final volume (600 mL). This solution was added to *n*-heptane (500 mL) with stirring, and the resulting mixture was concentrated under reduced pressure to a final volume (600 mL). *n*-Heptane (250 mL) was added to the resulting suspension, and the mixture was concentrated once again under reduced pressure to a final volume (600 mL). *n*-Heptane (400 mL) was added, and the suspension was heated to reflux to effect dissolution. After cooling to room temperature, the solids were collected by suction filtration, washed with *n*-heptane (100 mL), and dried at 45 °C under reduced pressure to give 45.0 g (68.3%, corrected, based on the chemical purity of **6**) of **6a** with a trans/cis isomer ratio of 121/1: mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 and 6.86 (d of d, J = 7.5 Hz, 4H), 7.33 (m, 3H), 7.16 (m, 2H), 5.05 (d, J = 11.9 Hz, 1H), 4.88 (m, 2H), 4.04 (q, J = 6.0 Hz, 2H), 3.75 (m, 1H), 3.43 (m, 1H), 1.83 (m, 2H), 1.56−1.07 (m, 7H), 1.44 (t, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H). Anal. Calcd for $C_{29}H_{43}NO_6SSi$: C, 62.00; H, 7.72; N, 2.49. Found: C, 61.93; H, 8.02; N, 1.99.

Phenylmethyl (*R*)-*trans*-α-[*N*-(4-Ethoxyphenylsulfonyl)amino]-4-propoxycyclohexaneacetate 8. Into a 1-L four-necked round-bottomed flask equipped with a mechanical stirrer, condenser, nitrogen inlet, addition funnel, and thermometer probe was placed **6a** (56.2 g, 0.100 mol) in dry acetonitrile (600 mL). The mixture was heated to 82 °C under atmospheric pressure, and acetonitrile (100 mL) was removed by distillation. The solution was allowed to cool to room temperature, and triethylsilane (17.5 g, 0.150 mol) was added over 5 min. In a separate flask, bismuth bromide (3.0 g, 0.0067 mol) was dissolved in acetonitrile (25 mL), and this solution was added to the solution of **6a** and triethylsilane over 5 min. Once the addition was complete, propionaldehyde (8.7 g, 0.150 mol) was introduced at such a rate that the reaction temperature did not exceed 30 °C. The reaction mixture was stirred for 30 min and quenched with a 5% solution of sodium bicarbonate (375 g). Ethyl acetate (320 mL) was added, and the suspension was filtered through Celite (10 g). The solids were washed with ethyl acetate (50 mL), and the filtrate and wash were combined and allowed to stand for 10 min to allow the layers to separate. The organic layer was washed with 1% sodium chloride solution (300 mL) and water (300 mL) and then concentrated under reduced pressure to a final volume (400 mL). To the resulting white suspension was added *n*-heptane (500 mL), and the solution was concentrated under reduced pressure to a final volume (300 mL). This was repeated two more times. To the suspension were added *n*-heptane (888 mL) and ethyl acetate (245 mL), and the mixture was heated to reflux (70 °C) to give a clear solution. The solution was cooled slowly to 0 °C and held at this temperature for 30 min. The solids were collected by suction filtration, washed with ethyl acetate/*n*-heptane (1/5 v/v, 190 mL), and dried at 45 °C under reduced pressure to give 41.5 g (84.8%, corrected) of **8** as a white solid: mp 108−111 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 and 6.87 (d of d, J = 8.3 Hz, 4H), 7.33 (m, 3H), 7.15 (m, 2H), 5.07 (d, J = 9.9 Hz, 1H), 4.88 (m, 2H), 4.04 (q, J = 6.6 Hz, 2H), 3.75 (m, 1H), 3.36 (t, J = 8.3 Hz, 2H), 3.08 (m, 1H), 2.02 (m, 1H), 1.62−1.05 (m, 12H), 0.89 (t, J = 8.3 Hz, 3H). Anal. Calcd for $C_{26}H_{35}NO_6S$: C, 63.78; H, 7.21; N, 2.86. Found: C, 63.62; H, 7.23; N, 2.33.

***trans*-(*R*)-[[*N*-(4-Ethoxyphenylsulfonyl)-*N*-(4-pyridinylmethyl)]amino]-4-propoxycyclohexanacetic Acid 9.** Into a 1-L three-necked round-bottomed flask equipped with a mechanical stirrer, condenser, nitrogen inlet, and thermometer probe were placed **8** (116.4 g, 0.24 mol), 4-picolyl chloride hydrochloride (58.8 g, 0.36 mol), powdered potassium carbonate (325 mesh) (310.1 g, 2.24 mol), and *N*,*N*-dimethylformamide (DMF) (357 mL). The slurry was stirred in a water bath at 18−22 °C, and tris[2-(2-methoxyethoxy)-ethyl]amine (TDA-1) (15.2 mL, 0.023 mol) was added in one portion. The slurry was stirred at room temperature for 24 h, and Celite (46.1 g) was added. After stirring for 10 min, the mixture was filtered using vacuum, and the filter cake was washed with toluene (3 × 225 mL). The filtrate and washes were combined and cooled to 5 °C, and 10% aqueous citric acid (715 mL) was added at such a rate that the temperature was kept below 20 °C. After stirring for 5 min, the layers were separated, and the aqueous layer was extracted with toluene (2 × 300 mL). All of the toluene fractions were combined and cooled below 5 °C. The cold toluene solution was washed sequentially with the following cold (5 °C) solutions: 3 N HCl (2 × 207 g), water (490 mL), and 3% aqueous sodium chloride (490 g). This was followed by washing the toluene solution at room temper-

ature with water (2 × 490 mL) and 25% aqueous sodium chloride solution (204 mL). The toluene solution was filtered through aluminum oxide (activated, acidic, Brockmann I, 121.3 g) using gravity. The alumina was washed with toluene (3 × 50 mL), and the combined fractions were concentrated under reduced pressure to a final volume (275 mL). The toluene solution containing the benzyl ester of **9** (109.5 g, 79% yield, determined by HPLC assay) was used as is in the following step. A sample of the solution was concentrated to an oil for charactization purposes: ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 3.8 Hz, 2H), 7.6 and 6.8 (d of d, J = 10.0 Hz, 4H), 7.34 (m, 3H), 7.26 (m, 2H), 7.24 (m, 2H), 4.9 (d, J = 11.3 Hz, 1H), 4.78 (d, J = 11.3 Hz, 1H), 4.63 (m, 2H), 4.32 (d, J = 11.3 Hz, 1H), 4.0 (m, 2H), 3.3 (m, 2H), 3.06 (m, 1H), 1.93 (m, 2H), 1.75 (m, 1H), 1.54 (m, 3H), 1.44 (m, 4H), 1.03 (m, 3H), 0.85 (t, J = 7.5 Hz, 3H), 0.75 (m, 1H); MS m/z 581 (M^+).

A toluene solution of the benzyl ester of **9** (475.5 g, 0.5 mol) was diluted with glacial acetic acid (1.4 L). The solution was concentrated under reduced pressure at 50 °C to a final volume (475 mL). The concentrate was diluted with glacial acetic acid (2.2 L), and a portion (1.4 L) was charged to a 2-L Parr bottle that had been inerted with hydrogen and which contained 10% Pd/C, 61.5% water wet (18.1 g). The mixture was hydrogenated under an atmosphere of 40 psi of hydrogen until the uptake slowed appreciably (approximately 60 min). The reaction mixture was treated with Celite (18.1 g) and stirred for 15 min. The suspension was filtered through a wet-packed pad of filter aid (42 g), and the filter cake was washed with glacial acetic acid (2 × 100 mL). The filtrate and washes were combined and concentrated under reduced pressure at 50 °C to a final volume (293 mL). This solution was added slowly to a stirred solution of sodium chloride (40.3 g) in water (2.05 L), which contained seed crystals of the desired product (**9**). When the addition was complete, the slurry was stirred for 10 min and then cooled to 2 °C and stirred at this temperature for 1 h. The solids were collected by suction filtration, washed with cold water (1.08 L), and dried at 55 °C under reduced pressure to give 69.6 g (54.5%, overall yield from **8**) of **9** as an off-white solid. The crude product (69.0 g) was dissolved in methanol (1.7 L) containing activated carbon (6.9 g) at reflux. After 1 h, the suspension was filtered through Celite (34.3 g), and the filter cake was washed with hot methanol (60 °C). The filtrate and wash were combined and concentrated under atmospheric pressure until the product began to crystallize (approximately 1 L of distillate was collected). The slurry was cooled to −10 °C and held for 1 h. The solids were collected by suction filtration, washed with cold methanol (−10 °C), and dried at 55 °C under reduced pressure to give 61.5 g (48.2%, overall yield from **8**) of **9** as a white solid: mp 206−208 °C; ^{1}H NMR (DMSO, d_6) δ 12.91 (br s, 1H), 8.48 and 7.37 (d of d, J = 5.0 Hz, 4H), 7.78 and 7.03 (d of d, J = 10.0 Hz, 4H), 4.62 (m, 2H), 4.10 (q, J = 6.2 Hz, 2H), 3.96 (d, J = 11.2 Hz, 1H), 3.25 (t, J = 7.50 Hz, 2H), 3.02 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.54 (m, 1H), 1.37 (m, 7H), 0.93 (m, 2H), 0.78 (t, J = 7.50 Hz, 3H), 0.75 (m, 1H), 0.52 (m, 1H); MS m/z 491 (M^+). Anal. Calcd for $C_{25}H_{34}N_2O_6S$: C, 61.20; H, 6.98; N, 5.71; S, 6.54. Found: C, 61.19; H, 6.92; N, 5.69; S, 6.48.

***trans*-(*R*)-[[*N*-(4-Ethoxyphenylsulfonyl)-*N*-(4-pyridinylmethyl)]amino]-*N*-hydroxy-4-propoxy-cyclohexaneacetamide Hydrochloride 10 (MMP090).** Into a 1-L four-necked round-bottomed flask equipped with a mechanical stirrer, condenser, nitrogen inlet, addition funnel, and thermometer probe was charged **9** (73.5 g, 0.15 mol), THF (750 mL), and DMF (1.2 mL). The slurry was cooled in an ice bath to 0−5 °C, and oxalyl chloride (23.9 g, 0.18 mol) was added at such a rate that the temperature did not exceed 5 °C. The time of the addition was 20 min. The homogeneous mixture was stirred at 0−5 °C for 1 h and then added via cannula to a cold (−15 °C), stirred solution of 50% aqueous hydroxylamine (198 g, 3.0 mol) in THF (2.25 L). The addition was carried out at such a rate that the temperature did not exceed −5 °C. After the addition was complete, the reaction mixture was allowed to warm to 0−5 °C and held at this temperature for 2 h. Ethyl acetate (750 mL) was added, and the lower aqueous layer was separated and discarded. The organic layer was concentrated under reduced pressure to a final volume (600 mL), and ethyl acetate (750 mL) was added. The solution was concentrated again in the same manner to a final volume (600 mL), and ethyl acetate (500 mL) was added. The ethyl acetate solution was washed with a 2% sodium tetraborate decahydrate solution (3 × 150 mL), water (150 mL), and 5% sodium chloride (150 mL) and concentrated under reduced pressure to a final volume (650 mL). Ethyl acetate (750 mL) was added, and the solution was concentrated to a final volume (550 mL) under reduced pressure. The process was repeated using ethyl acetate (500 mL) until a final volume (650 mL) was reached. After cooling to room temperature, absolute ethanol (130 mL) was added, and the solution was filtered using filter aid. The filtrate was heated to 55 °C, and 4.2 N ethanolic hydrogen chloride (23 mL, 96.6 mmol) was added. After seeding, the mixture was held at 55 °C for 20 min, and 4.2 N ethanolic hydrogen chloride (16 mL, 67.2 mmol) was added. Seed crystals were again added followed by ethyl acetate (115 mL). After stirring for 20 min, the mixture was cooled to 20 °C over 2 h and held at this temperature for an additional 2 h. The solids were isolated by suction filtration, washed with ethyl acetate (2 × 150 mL), and dried under reduced pressure at 50 °C overnight to give 60.3 g (74%) of MMP090 as an off-white solid: mp 140 °C (lit.[3] 131 °C); enantiomeric purity (HPLC assay) 100%; ^{1}H NMR (MeOD) δ 8.74 and 8.02 (d of d, J = 7.5 Hz, 4H), 7.78 and 7.05 (d of d, J = 9.0 Hz, 4H), 5.17 (d, 2H), 4.13 (q, J = 7.50 Hz, 2H), 3.90 (d, 1H), 3.40 (t, J = 6.0 Hz), 3.11 (m, 1H), 2.04 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.52 (m, 4H), 1.42 (t, J = 7.50 Hz, 3H), 1.11 (m, 3H), 0.89 (t, J = 7.5 Hz, 3H), 0.50 (m, 1H).

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