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Articles

Process Development of a Large-Scale Synthesis of TKA731: A Tachykinin Receptor Antagonist

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Abstract:

An efficient and chromatography-free large-scale synthesis of a tachykinin receptor antagonist TKA731 (1), utilizing the coupling of dipeptide 7 and 2-chloro-4(*3H*)-quinazolinone (13) as the key step, is described. The overall yield of 1 from BOC-L-3-(2-naphthyl)alanine (2) in six linear steps (total of eight steps) is 63%. This new convergent approach avoided the use of methyl iodide and the formation of methanethiol byproduct in the last step involving the construction of the quinazolinone ring in the original discovery synthesis. Four chromatographies were also eliminated. The main cause of the side reaction, leading to the urethane byproduct (I) formation and starting amino acid (2) liberation during the coupling of 2 with *N*-benzylmethylamine using well-known isobutyl chloroformate mediated mixed carboxylic-carbonic anhydride method, was found to be the symmetrical anhydride (III) formation from 2 as determined by the CO_2 offgas formation. A new procedure for the coupling of 2 with *N*-benzylmethylamine involving a reverse addition of 2 and the base to the coupling agent isobutyl chloroformate, followed by the addition of the amine, was developed that minimized the symmetrical anhydride formation. A novel, water-assisted *N*-methylation of 5 with dimethyl sulfate in the presence of sodium hydride in THF was also developed that eliminated the use of methyl iodide, silver oxide, and KCN. Deprotection of the BOC group in 6 with sulfuric acid circumvented the formation of diketopiperazine and tetrapeptide observed with HCl and trifluoroacetic acid, respectively.

Introduction

TKA731 (**1**) is a potent and selective antagonist for the human NK-1 tachykinin receptor.[1] It is targeted for the treatment of chronic inflammatory pain and diabetic neuropathy pain, and pain associated with angina, renal or billiary colic, and menstruation. The discovery synthesis of **1** is depicted in Scheme 1, which is a linear nine-step synthesis with four chromatographies. Coupling of BOC-L-3-(2-naphthyl)alanine (**2**) with *N*-benzylmethylamine in the presence of isobutyl chloroformate in dichloromethane gave intermediate **3**. Deprotection of Boc group in **3** with HCl gas in dioxane afforded the hydrochloride salt **4**. Coupling of the free base of **4** with Boc-L-proline in the presence of isobutyl chloroformate and 4-methylmorpholine in dichloromethane yielded dipeptide **5**. *N*-Methylation of dipeptide **5** was achieved with an excess of methyl iodide (8 equiv) and silver oxide (4 equiv) in DMF at 60 °C followed by workup using KCN. The resulting *N*-methylated derivative **6** was purified by silica gel chromatography. Deprotection of **6** with HCl gas in dioxane yielded amine **7**, that was then treated with 2-methoxycarbonyl phenyl isothiocyanate in dichloromethane to afford **8** in 90% yield after a chromatography. Saponification of the methyl ester **8** with 5 N aqueous NaOH in methanol afforded the acid **9**, which was treated with ammonium hydroxide in the presence of isobutyl chloroformate and 4-methylmorpholine in dichloromethane to furnish the amide **10** in 89% yield after a silica gel chromatography. The last step, involving the construction of the quinazolinone ring, was carried out by a treatment of **10** with an excess of methyl iodide in THF. Methanethiol was produced as the byproduct in this cyclization reaction. This afforded the drug substance **1** as an amorphous powder in only 43% yield after a silica gel chromatography. The overall yield of **1** was 31.6% from BOC-L-3-(2-naphthyl)-alanine (**2**).

Results and Discussion

At the onset of this project we decided to modify the discovery synthesis beyond intermediate **7** involving the construction of quinazolinone ring to produce **1**. This was because of three chromatographies, use of methyl iodide, methanethiol byproduct formation in the last cyclization step of the amide **10** to **1**, and poor yield. Thus, our goal was to

(1) Walpole, C. S. J.; Prashad, M.; Har, D. U.S. Patent 6,107,293, 2000.

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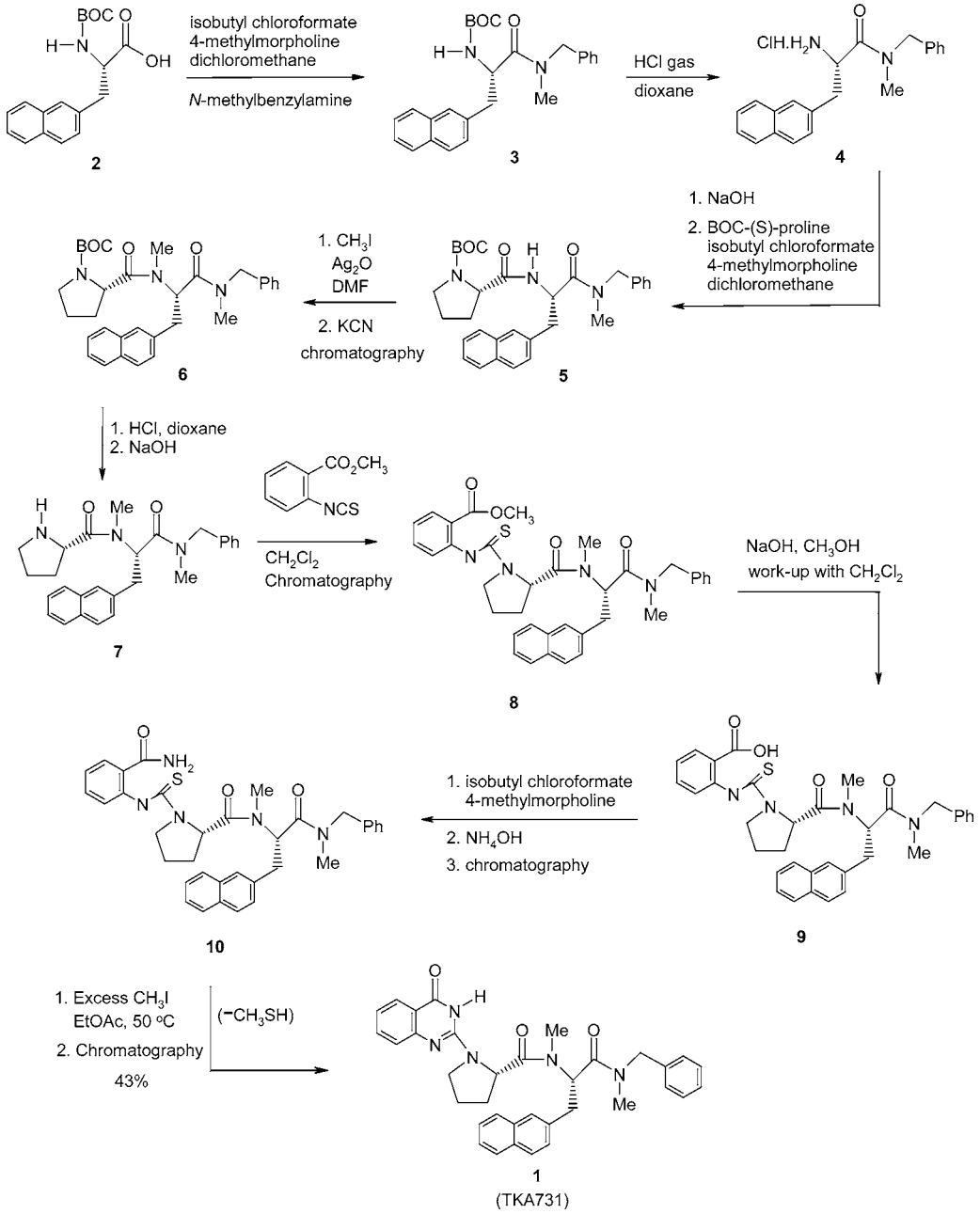
Scheme 1

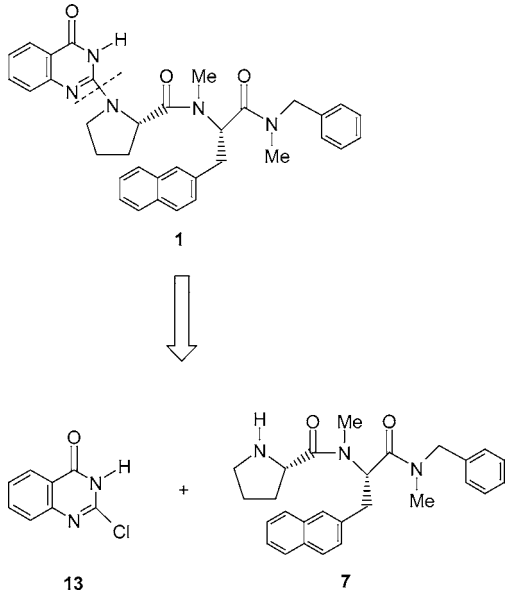


develop an efficient and convergent synthesis of **1** that would overcome these problems and would be practicable for large-scale preparation in our pilot plant. Our strategy, as illustrated in Scheme 2, was first to construct the quinazolinone ring with a leaving group at the 2-position, as in 2-chloro-4(*3H*)-quinazolinone (**13**),[2] and then couple[2,3] it with dipeptide **7** to afford the drug substance **1**.

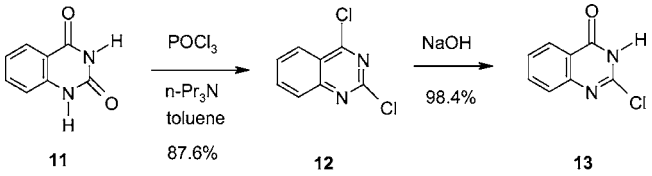
The synthesis of **13** from benzolyeneurea (**11**) was known in the literature.[4−6] It involved the dichlorination of **11** with phosphorus oxychloride to 2,4-dichloroquinazoline (**12**) followed by the selective hydrolysis of **12** with aqueous NaOH to **13**. However, scale-up of the known conditions[4] for the dichlorination of **11** using *N*,*N*-dimethylaniline and workup proved problematic since it led to the decomposition of **12** back to **11** during quenching of the reaction mixture and during the drying of the product. This prompted us to develop alternative reaction and workup conditions for this dichlorination step (Scheme 3).[6] Thus, reaction of benzoyl-eneurea (**11**) with phosphorus oxychloride (5 mL/g of **11**) in the presence of tripropylamine (2.15 equiv) at 102−105 °C for 3 h yielded a brown solution. Removal of phosphorus oxychloride by distillation and an azeotrope with toluene yielded a solution of 2,4-dichloroquinazoline (**12**) (Scheme 3) in toluene, which was quenched with water. Separation of the organic layer followed by washing with 5% sodium

(2) DeRuiter, J.; Brubaker, A. N.; Millen, J.; Riley, T. N. *J. Med. Chem.* **1986**, *29*, 627−629.
(3) Ogawa, N.; Yoshida, T.; Aratani, T.; Koshinaka, E.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2955−2967.
(4) Lacefield, W. B. U.S. Patent 3,956,495, 1976.
(5) Lange, N. A.; Roush, W. E.; Asbeck, H. J. *J. Am. Chem. Soc.* **1930**, *52*, 3696−3702.
(6) Scarborough, H. C.; Lawes, B. C.; Minielli, J. L.; Compton, J. L. *J. Org. Chem.* **1962**, *27*, 957−961.

Scheme 2



Scheme 3



hydroxide and water gave a neutral organic layer. Concentration of the organic layer and addition of heptane yielded 2,4-dichloroquinazoline (**12**) as a white solid in 75% yield. Hydrolysis of **12** with 2 N sodium hydroxide afforded pure 2-chloro-4(*3H*)-quinazolinone (**13**)[2] in 98% yield. Intermediate **13** is unstable at room temperature and must be stored in a refrigerator. One of the drawbacks with the preparation of 2,4-dichloroquinazoline (**12**) was the use of excess of phosphorus oxychloride and its removal by distillation. To circumvent these problems, we developed an improved process for the dichlorination of **11** that involved the treatment of **11** with phosphorus oxychloride (2.3 equiv) and tripropylamine (2.05 equiv) in refluxing toluene. The reaction mixture was quenched by reverse addition to water to furnish a biphasic mixture. Workup and concentration of the organic layer, and recrystallization of the crude product from heptane, afforded **12** in 87.6% yield.

The first two steps of the synthesis of intermediate dipeptide **7** were identical to those utilized in the synthesis of NKT343.[7,8] In connection with the synthesis of NKT343, we reported[9] the details of our early results on the process development of **4** from the coupling of BOC-L-3-(2-naphthyl)alanine (**2**) with *N*-benzylmethylamine in the presence of isobutyl chloroformate and 4-methylmorpholine in ethyl acetate under the well-known two-step conventional conditions, followed by the deprotection of **3** with HCl gas in ethyl acetate. Three issues needed to be addressed with the coupling conditions of **2** with *N*-benzylmethylamine for the large-scale synthesis of TKA731 (**1**). First, we had to replace 4-methylmorpholine with a base that could be extracted from the aqueous layer to address the disposal concerns with the aqueous layer. Second, to avoid a solvent exchange, ethyl acetate required replacement with a solvent that was compatible with aqueous HCl in the next deprotection step. Finally, since multiple additions of isobutyl chloroformate and *N*-benzylmethylamine were necessary to recycle in situ the liberated starting material **2** due to the urethane (**I**, Scheme 4) byproduct formation during the coupling reaction, and to drive the reaction to completion to **3**, our goal was also to develop a procedure that would avoid such multiple additions and make the procedure more convenient for large scale. Byproduct urethane **I** did not present any purification problems as it was easily removed in the mother liquor during the isolation of crystalline **4** after the deprotection step. Since the next deprotection step is carried out under acidic conditions in toluene, we decided to replace the ethyl acetate in the coupling step with toluene. 4-Methylmorpholine was replaced by *N*,*N*-dimethylbenzylamine as the base, because it could be easily extracted with heptane or toluene from the aqueous layer after basification (and recycled). The coupling reaction could also be satisfactorily carried out at −10 °C instead of −15 °C. Further optimization of the coupling reaction of **2** with *N*-benzylmethylamine proved to be quite interesting. The formation of the urethane byproduct **I** could either be due to the aminolysis at the undesired carbonyl[9,10−15] of the mixed carboxylic−carbonic anhydride intermediate **II** with *N*-benzylmethylamine, or due to the symmetrical anhydride **III** formation,[12] leaving unconsumed isobutyl chloroformate in the reaction mixture to react with *N*-benzylmethylamine (Scheme 4). In both cases, the reaction would also result in the liberation of the starting material **2**. To avoid the multiple additions of reagents and make the process more convenient for large scale, it became necessary for us to understand the mechanism of the urethane byproduct **I** formation and the liberation of the starting material **2**. We recently reported the development of a novel method using the formation of CO_2 offgas as the probe for elucidating the mechanism of the formation of **I** and liberation of the starting material **2**.[16,17] This method was based on the rationale that the symmetrical anhydride **III** formation would be accompanied by the formation of an equivalent amount of CO_2 during the first step involving the preparation of mixed carboxylic−carbonic anhydride **II** from **2**. This was because initially formed **II** can react further with **2**, present in excess,

(7) Ko, S. Y.; Walpole, C. WO 96/18643, 1996.
(8) Walpole, C.; Ko, S. Y.; Brown, M.; Beattie, D.; Campbell, E.; Dickenson, F.; Swan, S.; Hughes, G. A. Lemaire, M.; Lerpiniere, J.; Patel, S.; Urban, L. *J. Med. Chem.* **1998**, *41*, 3159−3173.
(9) Prashad, M.; Prasad, K.; Repič, O.; Blacklock, T. J.; Prikoszovich, W. *Org. Process Res. Dev.* **1999**, *3*, 409−415.
(10) Sole, N.; Torres, J. L.; Anton, J. M. G.; Valencia, G.; Reig, F. *Tetrahedron* **1986**, *42*, 193−198.
(11) Chen, F. M. F.; Lee, Y.; Steinauer, R.; Benoiton, N. L. *Can. J. Chem.* **1987**, *65*, 613−618.
(12) Chen, F. M. F.; Benoiton, N. L. *Can. J. Chem.* **1987**, *65*, 619−625.
(13) Thaler, A.; Seebach, D.; Cardinaux, F. *Helv. Chim. Acta* **1991**, *74*, 617−627.
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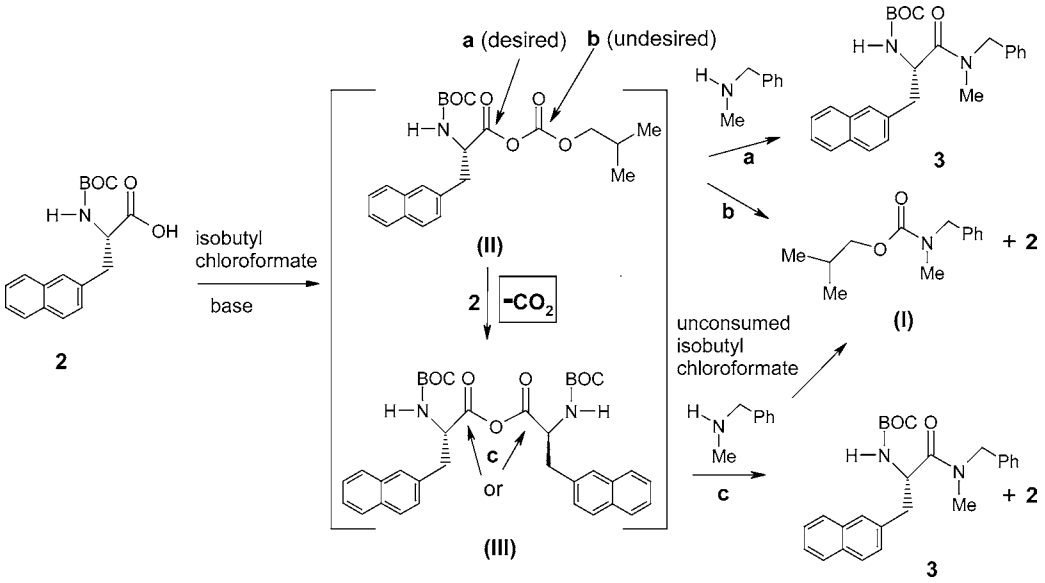
(15) Bodanszky, M.; Tolle, J. *Int. J. Pept. Protein Res.* **1977**, *10*, 380−384.
(16) Chaudhary, A.; Girgis, M. J.; Prashad, M.; Hu, B.; Har, D.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2003**, *44*, 5543−5546.
(17) Chaudhary, A.; Girgis, M. J.; Prashad, M.; Hu, B.; Har, D.; Repič, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 888−895.

Scheme 4



to afford the symmetrical anydride **III**, isobutanol, and CO_2, leaving some of isobutyl chloroformate unconsumed. Thus, if the CO_2 formation were observed during the formation of mixed carboxylic−carbonic anhydride **II** (before amine addition), then the urethane **I** would form as a result of the reaction of unconsumed isobutyl chloroformate with *N*-benzylmethylamine. Otherwise, its origin must be aminolysis at the undesired carbonyl in **II**. Thus, by quantifying the amount of CO_2 formed during the preparation of **II**, one can also determine whether there was any aminolysis at the undesired carbonyl in **II**. This would ascertain whether both effects are operating and to what extent. The reaction of **2** with isobutyl chloroformate in the presence of *N*,*N*-dimethylbenzylamine led to a significant amount of CO_2 formation, indicating the formation of 17.5% of symmetrical anhydride **III** along with **II**. Only a minor (<2.0%) amount of aminolysis at the undesired carbonyl in **II** was observed.[16,17] These results were consistent with the amount of liberated amino acid **2** at the end of the reaction as determined by HPLC. *Formation of substantial amounts of CO_2 in the first step clearly demonstrated that the formation of the urethane **I** and liberation of the starting material **2** was mainly due to the symmetrical anhydride **III** formation during the preparation of **II**.* No corresponding isobutyl ester of **2** was detected, suggesting that liberated isobutanol did not react with **II** to produce CO_2. *tert*-Butyloxycarbonyl protecting group on nitrogen is known[18] to prevent the formation of oxazolinone that would have resulted in CO_2 production from **II**. We reasoned that the symmetrical anhydride formation, and in turn the multiple additions of reagents to recycle in situ the liberated starting material **2**, could be avoided by reverting the order of addition of isobutyl chloroformate and **2**. One-stage conditions[19] involving the addition of isobutyl chloroformate to a solution of **2**, *N*-methylbenzylamine, and 4-methylmorpholine in THF led to ∼30% of **2**, again requiring multiple additions of isobutyl chloroformate to drive the reaction to completion. We have thus developed a new procedure that involves a reverse addition of **2** and *N*,*N*-dimethylbenzylamine in toluene to a solution of isobutyl chloroformate in toluene, followed by the addition of *N*-benzylmethylamine. These conditions led to completion of the reaction and avoided the multiple additions of isobutyl chloroformate. Only 1.9% of symmetrical anhydride **III** formed under these conditions during the reaction of **2** with isobutyl chloroformate as determined by CO_2 analysis and confirmed by measuring liberated **2**. Such a reverse addition of the amino acid to isobutyl chloroformate has not been reported previously in the peptide-coupling chemistry, and it represents a new methodology that is racemization free. These newly developed conditions were successfully scaled up in our pilot plant on 63.0-kg scale of **2**.

Our previously reported process for the deprotection of the BOC group in **3** utilized HCl gas in ethyl acetate.[9] The reaction mixture required concentration to remove HCl gas, and the hydrochloride salt **4** was isolated by filtration. Our goal was to avoid the use of HCl gas and the concentration of the reaction mixture on production scale. We found that the deprotection of the BOC group in **3** could be carried out with concentrated aqueous HCl at 65 °C in toluene. Only ∼1% of over-hydrolysis of the amide **3** to L-3-(2-naphthyl)-alanine was observed under these conditions. The hydrochloride salt that crystallized during the reaction was isolated by filtration. Thus, use of HCl gas and the concentration of the reaction mixture were eliminated. This afforded **4** in 93.4% yield (in two steps from **2**) with >99% purity and >99.5% enantiopurity. These deprotection conditions were successfully scaled up in the pilot plant with a crude solution of **3** in toluene from 63.0-kg scale of **2**.

Our improvements[7,9] of the discovery synthesis conditions for the coupling of the free base from **4** with BOC-L-proline with isobutyl chloroformate in ethyl acetate in the presence of 4-methylmorpholine cleanly afforded dipeptide **5** without any urethane byproduct formation that would be due to

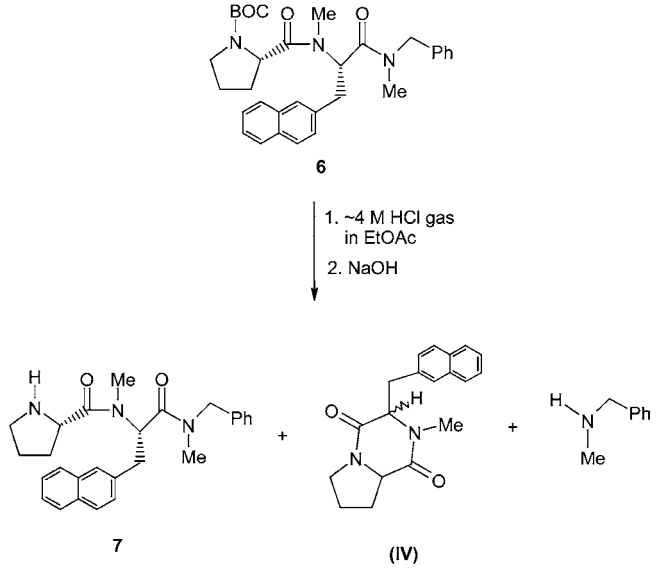
(18) Bodanszky, M.; Klausner, Y. S.; Ondetti, M. A., Eds. *Peptide Synthesis*; John Wiley & Sons: New York, London, Sydney, Toronto, 1976; pp 140.
(19) Shieh, W. C.; Carlson, J. A.; Shore, M. E. *Tetrahedron Lett.* **1999**, *40*, 7167−7170.

aminolysis of the wrong carbonyl group in mixed carboxylic−carbonic anhydride. We further optimized these conditions for the manufacturing scale. In an analogy to the coupling of **2** with *N*-benzylmethylamine, ethyl acetate was replaced by toluene and 4-methylmorpholine by *N*,*N*-dimethylbenzylamine. Thus, the free base from the HCl salt **4** was generated in toluene by a treatment with NaOH. The resulting solution of the free base **4** was used directly in the coupling reaction with BOC-L-proline in the presence of isobutyl chloroformate and *N*,*N*-dimethylbenzylamine to afford a solution of **5** in toluene. Since ∼40% of toluene was well tolerated in the next *N*-methylation step, crude **5** was used for *N*-methylation after concentration. These coupling conditions were successfully scaled up in the pilot plant on 33.0-kg scale of **4** to afford **5** in quantitative yield.

The next step was the *N*-methylation of dipeptide **5** to **6**. The discovery synthesis conditions were not suitable for scale-up in our pilot plant. The use of excess of methyl iodide (8.0 equiv) and silver oxide (4.0 equiv), followed by workup that involved distillative removal of methyl iodide using a −78 °C cold trap and washing with KCN, was both hazardous and uneconomical. Dimethyl sulfate was selected as the suitable methylating agent to replace methyl iodide because it is high boiling, and any excess of this reagent could be safely destroyed with ammonium hydroxide. We recently reported an efficient and practical *N*-methylation of amino acid derivatives with dimethyl sulfate in the presence of sodium hydride and a catalyic amount of water.[20] Reaction of water with sodium hydride generated highly reactive dry sodium hydroxide, which led to much faster reaction rates than powdered sodium hydroxide itself. No reaction was observed without water. Thus, *N*-methylation of crude **5** with dimethyl sulfate (1.8 equiv) in THF in the presence of sodium hydride (2.0 equiv) and catalytic amounts of water (>0.1 equiv) at 8−15 °C afforded the *N*-methylated dipeptide **6** in excellent yield which was used crude in the next step. The reaction mixture was quenched with ammonium hydroxide to destroy the excess of dimethyl sulfate and extracted with toluene. No epimerization was observed at 8−15 °C, however, ∼10% epimerization was observed at 30 °C. We found that any residual ethyl acetate in crude **5** inhibited the *N*-methylation, but 40% of toluene (of the desired volume of THF) in **5** did not affect the *N*-methylation.

It was imperative to optimize the above reaction around the amount of water and to further design *N*-methylation conditions that were addition-controlled to improve process safety for large scale. We determined the optimized amount of water to be 0.2 equiv (including residual water in **5** as determined by Karl Fischer analysis). The reaction was very slow with 0.125 equiv of water affording only 5% conversion in 2 h at 10 °C. With 0.165 equiv of water, the reaction was complete in 4 h, while with 0.2 equiv it required 2 h. Fastest reaction rates were observed with 0.25 equiv of water leading to completion of the reaction in 30 min. An excess of water (0.752 equiv) slowed the reaction as it required 4 h. The final reaction conditions utilized water (0.2 equiv), sodium hydride (1.7 equiv), and dimethyl sulfate (1.54 equiv) in THF at 10 °C for 3 h. Initially, the reaction was carried out by the sequential addition of water, a solution of **5** in THF, and dimethyl sulfate to a suspension of sodium hydride in THF and was scaled up to a multikilogram scale in the pilot plant. However, these reaction conditions were not addition-controlled. We recognized that the safest way to perform the *N*-methylation was to add a solution of **5**, dimethyl sulfate, and water in THF to a suspension of sodium hydride in THF. These addition-controlled conditions were found to be both safer and epimerization/racemization free as confirmed by a chiral HPLC.[20] Finally, **6** was isolated by a crystallization from a mixture of toluene and heptane in 86% yield with 99% purity and >99.5% enantiopurity. These *N*-methylation conditions were successfully scaled up in the pilot plant with a crude solution of **5** in toluene (containing 48.0 kg of **5**) obtained from 33.0-kg scale of **4** to afford **6** in 86.5% yield (in two steps from **4**).

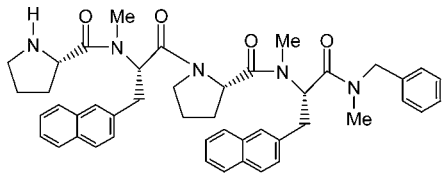
Scheme 5



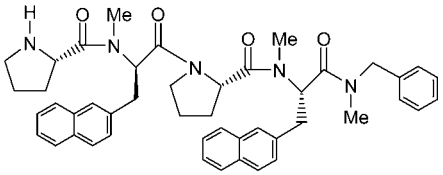
The discovery synthesis conditions for the deprotection of **6** to **7** utilized HCl gas in dioxane. Dioxane is a toxic solvent and was not deemed suitable for scale-up in our pilot plant. Further optimization proved particularly onerous. On the basis of our previous experience, dioxane was first replaced by ethyl acetate. The deprotection of **6** with HCl gas in ethyl acetate was satisfactory on a small scale; however, a scale-up of these conditions led to a significant loss in the yield (only 50%). Other byproducts, which were isolated by silica gel chromatography, were identified as diastereoisomers of diketopiperazine (**IV**, Scheme 5) formed by an intramolecular cyclization.[21] *N*-Benzylmethylamine was also isolated from this reaction. These results were in sharp contrast to those obtained with the deprotection of desmethyl analogue **5** in our NKT343 synthesis,[7,9] which gave excellent yield of the deprotected compound without the formation of any diketopiperazine byproducts. This marked difference in intramolecular transamidative cyclization behavior between **5** and **6** can be attributed to the differences

(20) Prashad, M.; Har, D.; Hu, B.; Kim, H. Y.; Repič, O.; Blacklock, T. J. *Org. Lett.* **2003**, *5*, 125−128.

(21) Dinsmore, C.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297−3312.



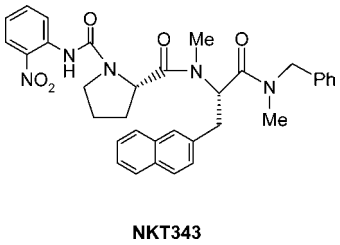
(V)



(VI)

Figure 1.

in the conformations of dipeptides **5** and **6** due to the *N*-methyl group. The intramolecular diketopiperazine formation from a dipeptide amide and an ester is known.[22] Dipeptide **6** was stable after its isolation. Formation of a mixture of two diastereomers of the diketopiperazine led us to speculate that chloride from HCl may be catalyzing this cyclization. We next investigated the deprotection of **6** with trifluoroacetic acid that gave satisfactory results. For early-phase development we had decided not to isolate the *N*-methylated intermediate **6** and use the toluene solution in the next deprotection step, as we had found that toluene was a suitable solvent for the deprotection. Thus, treatment of a solution of **6** in toluene with trifluoroacetic acid (7.5 equiv) followed by basification with aqueous sodium hydroxide, extractive workup with isopropyl acetate, and recrystallization from isopropyl acetate and heptane furnished **7** in 67% yield (overall from **4** in three steps) in high purity. The pH during basification required adjustment to 10−12 as below this pH, **7** was contaminated with its TFA salt. Scale-up of these conditions to a multikilogram scale in our pilot plant, however, led to the formation of a new tetrapeptide impurity (1.2%) that was a mixture of two diastereomers (**V** and **VI**; Figure 1) as indicated by LC−MS. The identity of one of the diastereomers was confirmed by comparison of its HPLC chromatogram with that of an authentic sample of **V** prepared from **7**. The quality of **7**, so obtained, afforded the drug substance **1** of the desired purity. Attempts to induce the



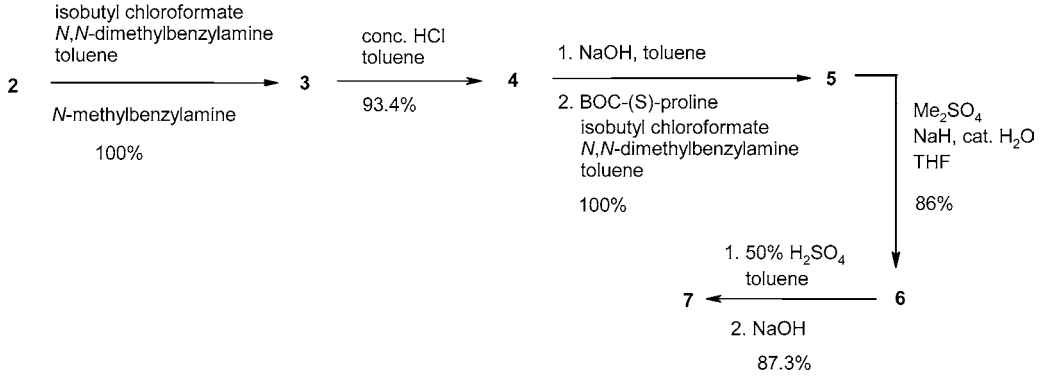
NKT343

Figure 2.

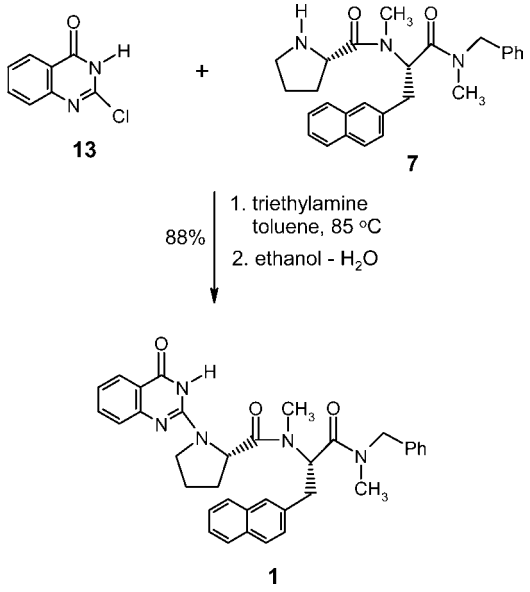
formation of tetrapeptide impurities **IV** in the laboratory experiments failed under a variety of conditions. Because of this problem and the fact that trifluoroacetic acid is not a preferred reagent in excess for manufacturing scale, we needed to develop alternative conditions for the deprotection of **6**. We next investigated the deprotection of **6** with sulfuric acid in toluene. No reaction was observed with 10% sulfuric acid at 55 °C; however, the deprotection was complete in 3 h with 50% sulfuric acid at 52 °C. Dilution of the reaction mixture with isopropyl acetate and basification with sodium hydroxide gave the organic layer, which was treated with heptane to afford crystalline **7** in 87.3% yield. The 1.0:2.0:6.0 ratio of toluene, isopropyl acetate, and heptane (per gram of the starting material **6** used) was important for the crystallization, and up to 4.0% of water was well tolerated. These conditions scaled up well in the pilot plant on 65.0-kg scale of **6** to afford **7** in 89.0% yield with excellent purity. No tetrapeptide impurities **V** and **VI** were detected by HPLC. The optimized synthesis of **7** for the large-scale is depicted in Scheme 6.

Before studying the coupling of dipeptide **7** and **13**, we first decided to develop a crystallization procedure for the drug substance **1**. This was because the drug substance **1** was initially an amorphous material, and it was purified by a silica gel chromatography both by the discovery chemists and us. Elimination of the silica gel chromatography was highly desirable for production scale. Additionally, the drug substance also retained solvents such as, ethyl acetate, toluene, and heptane. Initially, crystallization of **1** was effected from 2-propanol−water (1:1 v/v) and ethanol−water (1.25:1.0 v/v) using seeds[23] of analogous NKT343 (Figure 2),[9] affording crystalline TKA731 (**1**) as confirmed by X-ray powder diffraction. These seeds of **1** were then used in subsequent crystallizations. We decided to use the ethanol−water mixture for further work.

Scheme 6



Scheme 7



With two key intermediates **7** and **13** in hand, and having defined the conditions for the crystallization of TKA731 (**1**), we were ready to carry out the key and final coupling step. Having known that 2-chloro-4(*3H*)-quinazolinone (**13**) is unstable at room temperature as it hydrolyzes to benzoyleneurea (**11**), achieving a consistent quality of **13** could prove problematic. Thus, we needed to develop a robust process for this key coupling step of **7** with **13** that will tolerate the varying purity of **13** (due to varying amount of **11**). Since benzoyleneurea (**11**) is not soluble in toluene and can be easily removed by filtration, we selected toluene as the solvent for this coupling reaction. Thus, treatment of **7** with **13** (1.1 equiv) in toluene at 85 °C in the presence of triethylamine (1.5 equiv) afforded the reaction mixture that was filtered to remove triethylamine hydrochloride and any benzoyleneurea (**11**). The resulting toluene filtrate was washed with citric acid solution, water, and sodium bicarbonate to afford a solution of crude TKA731 (**1**). Concentration of the toluene solution followed by a solvent exchange with ethanol and crystallization from ethanol and water mixture (1.25:1.0 v/v) afforded pure and crystalline TKA731 (**1**) in 88% yield with >99.0% purity (Scheme 7). Thus, the silica gel chromatography used for **1** was eliminated. We found that **13** of the lower purity, containing up to 12% of **11**, afforded the drug substance **1** of the desired quality. These conditions were scaled-up in our pilot plant on a 23.4-kg scale of **7** to afford **1** in 89.1% yield with >99.5% purity.

To ascertain the enantiopurity of **1**, other three diastereoisomers of TKA731 (**VII**, **VIII**, and **IX**, Figure 3) were also synthesized from appropriate enantiomerically pure amino acids using the same synthesis. A chiral HPLC analysis of **1** suggested that product produced according to our optimized synthesis contained only 0.04% of D,L-isomer (**VIII**).

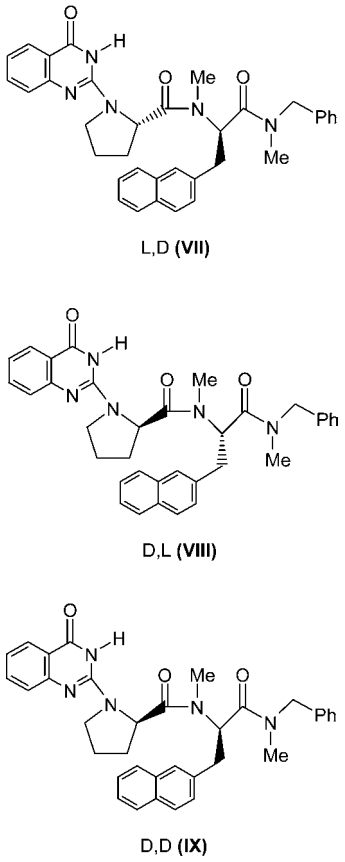


Figure 3.

Summary

An efficient and chromatography-free large-scale synthesis of a tachykinin receptor antagonist TKA731 (**1**), utilizing the coupling of dipeptide **7** and 2-chloro-4(*3H*)-quinazolinone (**13**) as the key step, is described. The overall yield of **1** from BOC-L-3-(2-naphthyl)alanine (**2**) in six linear steps (total of 8 steps) is 63%. This new convergent approach avoided the use of methyl iodide and the formation of methanethiol byproduct in the last step involving the construction of the quinazolinone ring in the original discovery synthesis. Four chromatographies were also eliminated. The main cause of the side reaction, leading to the urethane byproduct (**I**) formation and starting amino acid (**2**) liberation during the coupling of **2** with *N*-benzylmethylamine using well-known isobutyl chloroformate-mediated mixed carboxylic−carbonic anhydride method, was found to be the symmetrical anhydride **III** formation from **2** as determined by the CO_2 offgas formation. A new procedure for the coupling of **2** with *N*-benzylmethylamine involving a reverse addition of **2** and the base to the coupling agent isobutyl chloroformate, followed by the addition of the amine, was developed that minimized the symmetrical anhydride formation. A novel, water-assisted *N*-methylation of **5** with dimethyl sulfate in the presence of sodium hydride in THF was also developed that eliminated the use of methyl iodide, silver oxide, and KCN. Deprotection of the BOC group in **6** with sulfuric acid circumvented the formation of diketopiperazine and tetrapeptide observed with HCl and trifluoroacetic acid, respectively.

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Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-NMR spectrometer at 300 and 75 MHz, respectively. Melting points were measured on a Buchi 533 melting point apparatus. Enantiopurity of **1** was determined by a chiral HPLC method using a Phenomenex Chirex 3012, 4.6 mm × 150 mm column using a mixture of hexanes/1,2-dichloroethane/ethanol (50:15:5) as the mobile phase at a flow rate of 1.0 mL/min and UV detector (272 nm) at room temperature. The retention times of L,D (**VII**), D,L (**VIII**), D,D (**IX**) diastereoisomers and TKA731 (**1**) were 26.2, 33.8, 57.5, and 67.1 min, respectively.

BOC-(*S*)-3-(2-Naphthyl)alanyl-*N*-benzyl-*N*-methyl Amide (3). A Mettler-Toledo LabMax reactor, equipped with 1-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and distillation setup was charged with BOC-L-3-(2-naphthyl)alanine (**2**, 51.2 g, 162.3 mmol) and toluene (130.0 mL). The suspension was cooled to an internal temperature at 20 ± 2 °C, and *N*,*N*-dimethylbenzylamine (29.64 g, 219.3 mmol) was added over a period of 10 min, while maintaining the internal temperature at 20 ± 2 °C (jacket temperature 17 ± 3 °C). The addition funnel was washed with toluene (5.2 mL), and the wash was added to the reaction mixture. This solution was held for further use.

A Mettler-Toledo LabMax reactor, equipped with a clean 1-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and distillation setup was charged with toluene (390.0 mL) and isobutyl chloroformate (28.86 g, 211.3 mmol). The solution was cooled to an internal temperature of −12 ± 2 °C, and the above-prepared solution of BOC-L-3-(2-naphthyl)alanine (**2**) and *N*,*N*-dimethylbenzylamine in toluene was added over a period of 40 min, while maintaining an internal temperature at −12 ± 3 °C (jacket temperature −15 ± 3 °C). The addition funnel was washed with toluene (2 × 5.2 mL) and added to the reaction mixture. The slurry was stirred at −12 ± 2 °C for an additional 30 min, and a solution of *N*-benzylmethylamine (24.6 g, 203.0 mmol) in toluene (15.6 mL) was added over a period of 30 min, while maintaining an internal temperature at −12 ± 2 °C (jacket temperature −15 ± 3 °C). The addition funnel was washed with toluene (2 × 5.2 mL) and added to the reaction mixture. The reaction mixture was stirred at −12 ± 2 °C for 30 min and then warmed to an internal temperature at 21 ± 2 °C over a period of 35 min (the completion of the reaction was monitored by HPLC). The reaction mixture was quenched by addition of 1 N H_2SO_4 (125.0 mL) and stirred for 10 min. The organic layer was separated and washed sequentially with water (125.0 mL), 5% aqueous sodium bicarbonate (125.0 mL), and water (125.0 mL). The organic layer was concentrated at a jacket temperature of 65 ± 5 °C in vacuo (150 mbar) to collect 340 mL (∼309.0 g) of solvent and obtain a solution of BOC-(*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methyl amide in toluene (**3**, 310.0 mL, 272.0 g). This solution (containing 68.0 g of **3**, assumed 100% yield) was held at an internal temperature of 21−23 °C under nitrogen for the next step.

(This process was satisfactorily scaled up on 63.0-kg scale of BOC-L-3-(2-naphthyl)alanine in 100% assumed yield).

(*S*)-3-(2-Naphthyl)alanyl-*N*-benzyl-*N*-methylamide Hydrochloride (4). A Mettler-Toledo LabMax reactor, equipped with 2-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and a reflux condenser, was charged with a solution of BOC-(*S*)-3-(2-naphthyl)-alanyl-*N*-benzyl-*N*-methyl amide (**3**) in toluene (310.0 mL, 272.0 g) containing (68.0 g of **3**, 162.3 mmol). The solution was warmed to an internal temperature at 67 ± 3 °C (jacket temperature: 67−70 °C) over a period of 30 min, and concentrated hydrochloric acid (37%, 67.5 mL, 811.0 mmol) was added over a period of 45 min, while maintaining the internal temperature at 67 ± 3 °C (jacket temperature: 67−70 °C) to give a slurry. The reaction mixture was stirred at 67 ± 3 °C for an additional 8 h. The reaction mixture was cooled to an internal temperature at 20−23 °C over a period of 1 h and stirred for an additional 1 h at this temperature. The solids were collected by filtration, and the vessel was rinsed with toluene (100.0 mL), which was used to wash the filter cake. The filter cake was then washed with fresh toluene (50.0 mL) and dried at 60−65 °C in vacuo to afford (*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide hydrochloride (**4**, 53.8 g, 93.4% in two steps).[9] This intermediate is a weak-to-moderate skin sensitizer. The major byproduct in this deprotection step was *tert*-butyl chloride as determined by ^{1}H NMR and GC analysis of the toluene filtrate. About 10−11% of isobutene was also detected in offgases.

(This process was satisfactorily scaled up on 63.0-kg scale of BOC-L-3-(2-naphthyl)alanine (**2**) to afford 94% yield of **4** in two steps).

(2*S*)-2-[[[(1*S*)-2-[Methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid 1,1-Dimethylethyl Ester (5). A Mettler-Toledo LabMax reactor, equipped with a 1-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and distillation setup was charged with (*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide hydrochloride (**4**, 65.8 g, 185.4 mmol) and toluene (400.0 mL). To the stirring suspension was added 5% sodium hydroxide solution (280.0 mL, 294.6 g) over a period of 10 min, while maintaining the internal temperature at 22 ± 3 °C. The suspension was stirred for 1 h until all the solids dissolved. The organic layer was separated, washed with 20% sodium chloride solution (140.0 mL, 158.0 g), and filtered through a line filter. The vessel was washed with toluene (28.0 mL), and the wash was line filtered and mixed with the batch. The combined filtrates were concentrated in vacuo (150 ± 10 mbar) at an internal temperature of 57 ± 5 °C (jacket temperature: 68 ± 3 °C) to collect 320−350.0 mL of solvent to obtain (*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide free base (140.0 mL, 135.5 g). This solution was held for further use.

A Mettler-Toledo LabMax reactor, equipped with a 1-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and distillation setup was charged with BOC-L-proline (42.3 g, 196.5 mmol) and toluene (295.0 mL). To the stirring suspension was added

N,*N*-dimethylbenzylamine (33.8 g, 250.0 mmol) over a period of 10 min, while maintaining the internal temperature at 22 ± 3 °C (jacket temperature: 20 ± 3 °C). The addition funnel was washed with toluene (6.0 mL), and the wash was added to the reaction mixture. The reaction mixture was stirred to obtain a clear solution. The solution was cooled to an internal temperature at −12 ± 3 °C (jacket temperature: −15 ± 3 °C), and isobutyl chloroformate (27.1 g, 198.4 mmol) was added over a period of 30 min, while maintaining the internal temperature at −12 ± 3 °C (jacket temperature: −15 ± 3 °C). The addition funnel was washed with toluene (3 × 4.0 mL), and the washes were added to the reaction mixture. The resulting suspension was stirred at an internal temperature at −12 ± 3 °C (jacket temperature: −15 ± 3 °C) for an additional 30 min. The above prepared solution of (*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide free base (140.0 mL, 135.5 g) was then added at a constant rate over a period of at least 60 min, while maintaining the internal temperature at −12 ± 3 °C (jacket temperature: −15 ± 3 °C). The addition funnel was washed with toluene (3 × 6.0 mL), and the washes were added to the reaction mixture. The reaction mixture was stirred at this temperature for an additional 30 min and then warmed to an internal temperature at 22 ± 3 °C over a period of 45 min. The reaction mixture was stirred at an internal temperature of 22 ± 3 °C for an additional 15 min, and 1 N sulfuric acid (180.0 mL) was added to the reaction mixture, while maintaining the internal temperature at 22 ± 3 °C. The stirring was continued for an additional 5−10 min, and the organic layer was separated. The organic layer was washed sequentially with water (180.0 mL), 8% aqueous sodium bicarbonate (180.0 mL), and water (180.0 mL). The organic layer was concentrated in vacuo (150 ± 10 mbar) at an internal temperature at 55 ± 5 °C (jacket temperature: 68 ± 3 °C) to collect 340−370 mL of solvent to obtain (2*S*)-2-[[[(1*S*)-2-[methyl(phenylmethyl)-amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester (**5**, 145.0 mL, 149.0 g containing 95.6 g of **5** based on 100% theoretical yield). This solution was held at an internal temperature of 21−23 °C under nitrogen for further use.

(This process was scaled-up on 33.0-kg scale of **4** in 100% assumed yield of **5**).

(2*S*)-2-[[Methyl[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (6). A Mettler-Toledo LabMax reactor, equipped with a 1-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and distillation setup was charged with sodium hydride (6.188 g, 154.7 mmol, 60% dispersion in mineral oil) and tetrahydrofuran (295.0 mL). To the suspension, cooled to an internal temperature at 10 ± 3 °C, was added a solution of crude (2*S*)-2-[[[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester solution (**5**, containing 46.93 g product, 91.0 mmol) as prepared above, tetrahydrofuran (90.9 mL), dimethyl sulfate (17.71 g, 140.4 mmol), and of water (0.3276 g, 18.2 mmol) over a period of 1 h while maintaining an internal temperature at 10 ± 3 °C. The addition funnel was washed with tetrahydrofuran (3 × 4.9 mL), and the washes were added to the reaction mixture. The reaction mixture was stirred at an internal temperature of 10 ± 3 °C for 3 h. Ammonium hydroxide (28−30%, 54.6 mL, 49.14 g) was added to the reaction mixture over a period of 30 min, while maintaining the internal temperature at 10 ± 3 °C. The mixture was stirred at this temperature for 1 h, and water (72.6 mL) and toluene (182.0 mL) were added. After stirring for 10 min at 20 ± 3 °C, the organic layer was separated and washed with water (91.0 mL). The organic layer was concentrated in vacuo (150 ± 10 mbar) at an internal temperature of 28−45 °C (jacket temperature 33−49 °C) to collect ∼ 375 mL of solvent to obtain a solution of crude (2*S*)-2-[[methyl[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester (**6**, 220.0 mL) in toluene. This solution was heated to an internal temperature of 57 ± 2 °C (jacket temperature 62−64 °C) over a period of 10 min, and heptane (392.7 mL) was added over a period of 30 min, while maintaining the internal temperature at 57 ± 2 °C (jacket temperature 59−62 °C). Immediately, pure (2*S*)-2-[[methyl[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester (**6**) seeds (35.3 mg) were added, and the mixture was cooled to an internal temperature of 21 ± 2 °C (jacket temperature 18−22 °C) over a period of 1 h, and the stirring was continued at this temperature for an additional 10 h. The solids were collected by filtration. The vessel and filter cake were washed with a mixture of toluene and heptane (1:5 v/v, 500.0 mL). The filter cake was washed with a fresh mixture of toluene and heptane (1:5 v/v, 59.0 mL) in two equal portions of 29.5 mL each. The solid was dried at 45−50 °C in vacuo to obtain pure (2*S*)-2-[[methyl[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester (**6**, 41.4 g, 86.0% in two steps): mp 126−129 °C; ^{1}H NMR ($CDCl_3$) mixture of rotamers δ 1.71−2.23 (m, 4H), 2.31−2.52 (m, 9H), 2.67−2.76 (m, 3H), 2.77−3.07 (m, 1H), 3.08−3.23 (m, 3H), 3.30−3.75 (m, 3H), 4.24−4.72 (m, 3H), 5.78−5.95 (m, 1H), 6.59−6.79 (m, 2H), 6.83−7.12 (m, 3H), 7.33−7.48 (m, 3H), 7.65−7.82 (m, 4H); $[\alpha]_d$ −177.3 (c = 2.54, CH_3OH); Calc for $C_{32}H_{39}N_3O_4$: C, 72.50; H, 7.36; N, 7.93%. Found: C, 72.39, H, 7.53; N, 7.92%.

(This process was scaled up on 48.0-kg scale of crude **5** obtained from 33.0 kg of **4** to afford 86.5% yield of **6** in two steps).

***N*-Methyl-*N*-[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]-(2*S*)-2-pyrrolidnecarboxamide (7).** A Mettler-Toledo LabMax reactor, equipped with a 1-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and distillation setup was charged with (2*S*)-2-[[methyl[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester (**6**, 60.0 g, 113.27 mmol) and toluene (60.0 mL). The suspension was heated to an internal temperature of 78 ±

3 °C (jacket temperature = 83 ± 3 °C) over a period of 1 h to obtain a clear solution. The resulting solution was cooled to an internal temperature of 53 ± 3 °C over a period of 30 min, and 50% sulfuric acid (66.0 g) was added over a period of 40 min, while maintaining the internal temperature at 53 ± 3 °C (mild exothermic reaction with gas evolution). The mixture was stirred at this temperature for an additional 2−4 h. The mixture was cooled to an internal temperature of 17 ± 3 °C over a period of 30 min, and water (120.0 mL) and isopropyl acetate (120.0 mL) were added sequentially. The mixture was stirred at 17 ± 3 °C for 5 min, and 10% sodium hydroxide solution (300.0 g) was added over a period of 40 min to adjust the pH to 11−13, while maintaining an internal temperature at 17 ± 3 °C. After the mixture stirred at this temperature for 10 min, the organic layer was separated and washed with 10% sodium chloride solution (60.0 g). The organic layer was line-filtered to a clean Mettler-Toledo LabMax reactor, equipped with 1-L glass vessel, pitched-blade impeller, RTD sensor, addition funnel, nitrogen inlet/outlet, and reflux condenser. The solution was heated to an internal temperature of 83 ± 3 °C over a period of 60 min, and heptane (360.0 mL) was added over 40 min, while maintaining the internal temperature above 75 °C. The mixture was cooled at a rate of 0.5 °C/min, and pure *N*-methyl-*N*-[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]-(2*S*)-2-pyrrolidnecarboxamide seeds (**7**, 36.0 mg) were added at an internal temperature of 66 ± 3 °C. The mixture was cooled to an internal temperature of 22 ± 3 °C over a period of 1 h and 30 min (cooling rate = 0.5 °C/min), and the stirring was continued at this temperature for an additional 14 h. The solids were collected by filtration, washed with a mixture of isopropyl acetate and heptane (1:4 v/v; 80.0 mL) in two equal portions of 40.0 mL each, and dried at 45−50 °C in vacuo to afford pure *N*-methyl-*N*-[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]-(2*S*)-2-pyrrolidnecarboxamide (**7**, 42.5 g, 87.3%) as a white solid: mp 117−120 °C; ^{1}H NMR ($CDCl_3$) mixture of rotamers δ 1.26−2.12 (m, 4H), 2.59−3.17 (m, 8H), 3.48−3.89 (m, 2H), 4.36−4.81 (m, 2H), 5.89−6.05 (m, 1H), 6.69−6.90 (m, 2H), 6.92−7.16 (m, 3H), 7.30−7.49 (m, 3H), 7.63−7.79 (m, 4H); $[\alpha]_d$ −147.5 (c = 2.92, CH_3OH); Calc for $C_{27}H_{31}N_3O_2$: C, 75.43; H, 7.22; N, 9.78%. Found: C, 75.35, H, 7.37; N, 9.81%.

This intermediate is a skin sensitizer. The major byproduct in this deprotection step was *tert*-butyl alcohol as determined by ^{1}H NMR of the toluene layer after the reaction.

(This process was satisfactorily scaled-up on 65.0-kg scale of **6** to afford 89% yield of **7**).

2,4-Dichloroquinazoline (12). A 5-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, condenser with nitrogen inlet−outlet and heating mantle was charged with benzoyleneurea (**11**, 200.0 g, 1.233 mol) and toluene (800.0 mL). Phosphorus oxychloride (435.0 g, 2.84 mol) was added with stirring at 20 °C, and the addition funnel was washed with toluene (10.0 mL), which was added to the reaction mixture. After stirring at 20 °C for 15 min, the mixture was heated to an internal temperature of 55 °C, and tripropylamine (363.0 g, 2.53 mol) was added over a period of 1 h at a rate that maintains the internal temperature below 65 °C (an exothermic reaction). The addition funnel was washed with toluene (10.0 mL), and the wash was added to the reaction mixture. The mixture was slowly heated to an internal temperature of 85 °C, and after 10 min, to 108−110 °C. The mixture was stirred at 108−110 °C for 4 h to obtain a clear brown-yellow solution. The reaction mixture was cooled to an internal temperature of 40 °C and added to warm (35−40 °C) water (1.5 L) with nitrogen pressure over a period of 30−40 min, while maintaining an internal temperature below 45 °C. The first vessel was washed with toluene (0.8 L) and added to the reaction mixture. After stirring for an additional 30 min, the bottom aqueous layer was discarded, and the organic layer (with rag layer) was filtered over Cellflock-Polster (20.0 g). The filter cake was washed with toluene (20.0 mL) and water (40.0 mL). The aqueous layer was removed from the combined filtrates, and the organic layer was washed with water (2 × 400.0 mL) (the pH of the aqueous layer was >3). The organic layer was dried by azeotropic removal of water at 70 °C (external temperature) under vacuum (200 mbar). The organic layer was concentrated at 55 °C (external temperature) under vacuum (50 mbar) until no more solvent distilled. To the residue was added heptane (2.4 L), and the mixture was heated to an internal temperature at 90 °C to obtain a brown solution. The solution was cooled to an internal temperature at 70 °C, and seeds of 2,4-dichloroquinazoline (**12**, 0.2 g) were added. The mixture was slowly cooled to room temperature (21−23 °C) and stirred at this temperature for ∼14 h. The mixture was cooled to 0−10 °C and stirred at this temperature for 1 h. The solid was collected by filtration, washed with heptane (450.0 mL), and dried at 40 °C in vacuo to afford pure 2,4-dichloroquinazoline (**12**, 251.0 g, 87.6%): mp 118−120 °C.[4] Store this material in a refrigerator.

2-Chloro-4(3H)-quinazolinone (13). A 3-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet−outlet, and cooling bath was charged with a solution of sodium hydroxide (2 N, 840.0 mL). The solution was cooled to an internal temperature at 17−19 °C, and 2,4-dichloroquinazoline (**12**, 112.0 g, 562.7 mmol) was added in three equal portions of 37.33 g each at 10−15 min intervals. The resulting slurry was stirred at 21−24 °C for 4 h to obtain a solution. Water (560.0 mL) was added over 5−10 min, while maintaining the internal temperature at 21−24 °C. After stirring for 5−10 min, glacial acetic acid (140.0 mL) was added with efficient stirring over 20−25 min, while maintaining the internal temperaure at 21−24 °C. The solid was collected by filtration, washed with water (3 × 400 0.0 mL), and dried at 50−52 °C under vacuum for 24 h (to obtain a constant weight) to afford pure 2-chloro-4(*3H*)-quinazolinone (**13**, 100.0 g, 98.4%) as a white solid: mp 219−221 °C.[2]

Coupling of 7 and 13. *(2S)-1-(3,4-dihydro-4-oxo-2-quinazolinyl)-N-methyl-N-[(1S)-2-[methyl(phenylmethyl)-amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]-2-pyrrolidin-ecarboxamide (**1**).* A Mettler-Toledo LabMax reactor, equipped with a 1-L glass vessel, pitched-blade impeller, RTD sensor,

addition funnel, nitrogen inlet/outlet, and distillation setup was charged with (2*S*)-*N*-methyl-*N*-[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]-2-pyrrolidinecarboxamide (**7**, 42.96 g, 100.0 mmol), 2-chloro-4(*3H*)-quinazolinone (**13**, 19.87 g, 110.0 mmol), toluene (644.0 mL), and triethylamine (15.18 g, 150.0 mmol). The suspension was heated to an internal temperature at 85 ± 2 °C over a period of 1 h and stirred at this temperature for an additional 2.5 h. The reaction mixture was cooled to an internal temperature at 20−25 °C over a period of 1 h and stirred at this temperature for additional 30 min. The reaction mixture was filtered, and the filter cake was washed with toluene (2 × 65.0 mL). The combined filtrates were sequentially washed with 20% citric acid solution (100.0 mL), water (100.0 mL), 8% aqueous sodium bicarbonate solution (100.0 mL), and water (100.0 mL). The organic layer was line-filtered. The separatory funnel was washed with toluene (20.0 mL), and the wash was combined with the filtered organic layer. The organic layer was transferred to a 2-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet−outlet, and heating mantle and concentrated in vacuo to collect ∼660 mL of solvent to obtain less than 140 mL of a solution. Ethanol (920.0 mL, 200 proof) was added, and the solution was concentrated in vacuo to collect ∼500 mL of solvent to obtain a solution or light slurry (∼550 mL). This process was repeated twice more with 400.0 mL of ethanol (200 proof) each time to collect ∼400.0 mL of solvent each time to obtain a light slurry (∼550 mL). The reaction mixture was heated to an internal temperature at 73−78 °C (external temperature 85−95 °C) over a period of 15 min to obtain a clear solution (Note: adjust the volume to approximately 550 mL.), and water (400.0 mL) was added over a period of 30 min, while maintaining an internal temperature at 72−78 °C. The solution was cooled to an internal temperature at 20−25 °C over a period of 2 h with efficient stirring. A solid crystallized at ∼65 °C. The resulting suspension was stirred at 20−25 °C for an additional 6 h. The solids were collected by filtration, washed with a mixture of ethanol and water (1:1 v/v; 480.0 mL) in two equal portions of 240 mL each, dried at 60−65 °C in vacuo to afford pure (2*S*)-1-(3,4-dihydro-4-oxo-2-quinazolinyl)-*N*-methyl-*N*-[(1*S*)-2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]-2-pyrrolidinecarboxamide (**1**, 50.96 g, 88%): mp 175−176 °C; ^{1}H NMR ($CDCl_3$) mixture of rotamers δ 1.80−2.30 (m, 4H), 2.68 (s, 0.59 × 3H, major N-CH_3), 2.74 (s, 0.41 × 3H, minor N-CH_3), 2.80−3.0 (m, 1H), 3.35 (m, 3H), 3.50−3.90 (m, 3H), 4.33 (d, 1H, J = 14.9 Hz), 4.45−4.52 (m, 1H), 4.86 (m, 0.41 × 1H, minor CH), 5.0 (m, 0.59 × 1H, major CH), 5.80 (m, 1H), 6.60−7.70 (m, 15H), 7.95 (m, 1H), 10.60 (bs, 1H); $[\alpha]_d$ −255.8 (c = 1.0, CH_3OH); Calc for $C_{35}H_{35}N_5O_3$: C, 73.28; H, 6.15; N, 12.21%. Found: C, 72.91, H, 6.28; N, 12.13%.

(This process satisfactorily scaled-up on 23.4-kg scale of **7** to afford 89% yield of **1**).

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