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Efficient Synthesis of NK_1 Receptor Antagonist Aprepitant Using a Crystallization-Induced Diastereoselective Transformation†

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Abstract: An efficient stereoselective synthesis of the orally active NK_1 receptor antagonist Aprepitant is described. A direct condensation of *N*-benzyl ethanolamine with glyoxylic acid yielded a 2-hydroxy-1,4-oxazin-3-one which was activated as the corresponding trifluoroacetate. A Lewis acid mediated coupling with enantiopure (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol afforded a 1:1 mixture of acetal diastereomers which was converted into a single isomer via a novel crystallization-induced asymmetric transformation. The resulting 1,4-oxazin-3-one was converted via a unique and highly stereoselective one-pot process to the desired α-(fluorophenyl)morpholine derivative. Interesting and unexpected [1,2]-Wittig and [1,3]-sigmatropic rearrangements were identified during the optimization of these key steps. In the final step, a triazolinone side chain was appended to the morpholine core. The targeted clinical candidate was thus obtained in 55% overall yield over the longest linear sequence.

Introduction

The tachykinins, substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) are related neuropeptides with a common C-terminal sequence which are widely distributed in the peripheral and central nervous systems where they act as neurotransmitters and neuromodulators.[1] Three receptor subtypes have been confirmed by the cloning of three distinct genes from various mammalian sources, including man, with SP being the preferred agonist for the NK_1 receptor, NKA for the NK_2 receptor and NKB for the NK_3 receptor.[2] The advent of selective non-peptide NK receptor antagonists has contributed significantly to the understanding of neurokinin receptor pharmacology and the physiological role of the tachykinins.[3] The NK_1 receptor antagonists have received most of the attention and compounds have been evaluated for a wide variety of important medical disorders. Research at Merck has led to the identification of Aprepitant (**1**) as a potent and orally active NK_1 receptor antagonist for clinical evaluation in chemotherapy-induced emesis,[4] depression[5] and other potential indications. An efficient and practical synthesis for **1** was clearly needed in support of these studies.[6]

Compound **1** contains an unusual *cis*-2-alkoxy-3-arylmorpholine core structure featuring three stereogenic centers in close proximity. An initial logical disconnection of the strategic acetal bond in **2** suggested enantiomerically pure **3** and **4** as key intermediates (Scheme 1). However, this glycosidation-type approach did not prove to be viable. Numerous methods for activation of **3** (LG = leaving group) in two protecting group series (P = Bn or BOC) together with a large number of solvent and Lewis acid combinations were evaluated with little success.[7] In all cases, the stereoselectivity in favor of the desired **2** was

† Dedicated to Prof. Andrew S. Kende on the occasion of his 70th birthday.

‡ Department of Molecular Design and Diversity, Merck Research laboratories.

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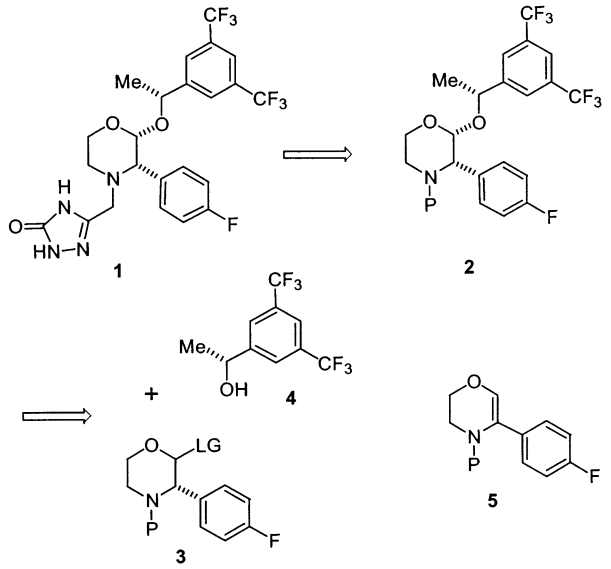
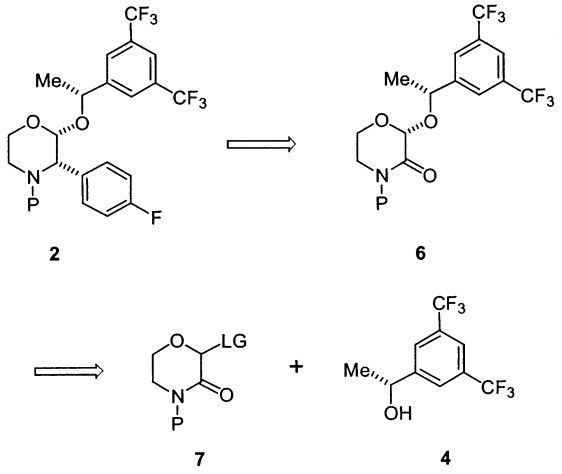
10.1021/ja027458g CCC: $25.00

Scheme 1



Scheme 2



modest at best. Significant amounts of elimination product **5** (P = Bn or BOC) were also formed. Recently, some of us reported on a synthesis of **1** which uses an intramolecular glycosidation reaction to circumvent these difficulties.[8] This paper will report on the successful implementation of a different approach.

Our analysis is presented in Scheme 2. The retrosynthetic introduction of a lactam carbonyl group was expected to perform two important functions in this strategy. Substitution reactions at C-2 in **7** with the poorly nucleophilic **4** should be facilitated and β-elimination would no longer be possible as a result of C-3 being sp^2 hybridized. High levels of diastereoselectivity were not anticipated for the coupling between racemic **7** and enantiopure **4**. However, a high-yielding stereoselective transformation could in principle be achieved if conditions were identified under which **6** and its C-2 epimer were induced to equilibrate, aided by the neighboring carbonyl group, at a rate which is competitive with the selective crystallization of the desired diasteromer. Crystallization-induced asymmetric transformations[9] have been reported in the literature and are most often based on serendipitous discoveries.[10] Most of these deal with salts and other complexes, often of amino acids and their derivatives.[11] Transformations of this kind involving covalent diastereomers are less common. Several cases have been reported in which compounds containing a chiral auxiliary, which must be removed at a later stage, were used.[12] This paper will describe a rare example of a crystallization-induced diastereoselective transformation which was designed to make use of a stereocenter that is an integral part of the desired target. As a corollary to this approach, the development of a novel and efficient conversion of **6** to **2** was also required. The successful accomplishment of these two goals are at the heart of an efficient and practical synthesis of NK_1 receptor antagonist **1**.

Results and Discussion

Synthesis of *N*-Benzyl Lactam Lactol 9. The choice for protecting group P in Scheme 2 was in large part dictated by the chemistry needed to convert **6** to **2** (Scheme 2). This requires (at least formally) a reduction step. To achieve maximum efficiency late in the synthesis, we decided to use a benzyl protecting group hoping that deprotection and reduction could be achieved in the same step. Lactam lactol **9** could be prepared in two steps from inexpensive *N*-benzylethanolamine (Scheme 3). Condensation of **8** with diethyl oxalate yielded the expected lactam lactone **10**.[13,14] Lithium tri(*sec*-butyl)borohydride reduction of the latter afforded **9** in high yield.

The need for an oxidation state adjustment in this approach was not ideal and a more direct synthesis for **9** was therefore pursued. The literature suggested that condensation of *N*-benzylethanolamine (**8**) with an alkyl glyoxylate or the corresponding hemiacetal could furnish **9** directly.[15] However, in our

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(12) For some recent examples: (a) Komatsu, H.; Awano, H. *J. Org. Chem.* **2002**, *67*, 5419−5421. (b) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130−5131. (c) Boesten, W. H. J.; Seerden, J.-P. G.; de Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L. M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 1121−1124. (d) Lee, S.-k; Lee, S. Y.; Park, Y. S. *Synlett* **2001**, 1941−1943. (e) Vedejs, E.; Donde, Y. *J. Org. Chem.* **2000**, *65*, 2337−2343. (f) Vedejs, E.; Chapman, R. W.; Lin, S.; Muller, M.; Powell, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 3047−3052. (g) Silverberg, L. J.; Kelly, S.; Vemishetti, P.; Vipond, D. H.; Gibson, F. S.; Harrison, B.; Spector, R.; Dillon, J. L. *Org. Lett.* **2000**, *2*, 3281−3283. (h) Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293−9294. (i) Shieh, W.-C.; Carlson, J. A.; Zaunius, G. M. *J. Org. Chem.* **1997**, *62*, 8271−8272. (j) Caddick, S.; Jenkins, K. *Tetrahedron Lett.* **1996**, *37*, 1301−1304. (k) Hagman, W. K. *Synth. Comm.* **1986**, *16*, 437−440. (l) Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227−236.

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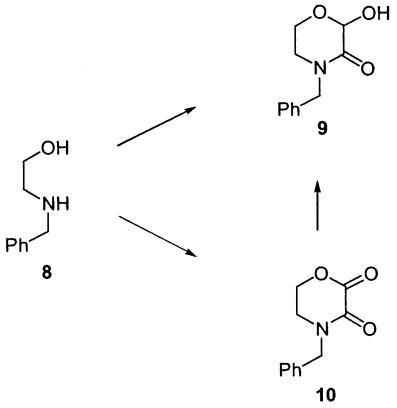
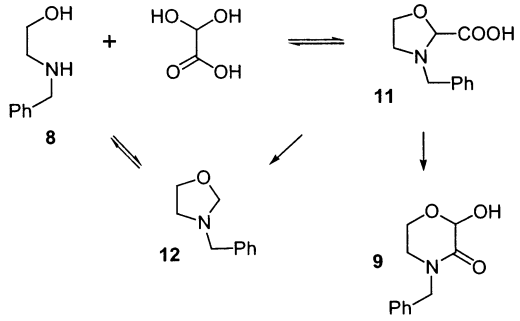
(14) Drefahl, G.; Hartmann, M.; Skurk, A. *Chem. Ber.* **1966**, *99*, 2716−2717.

Scheme 3



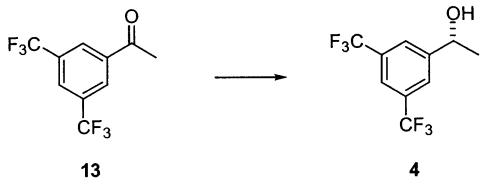
Scheme 4



hands the reaction of **8** with commercially available methyl 2-hydroxy-2-methoxy acetate afforded **9** in a meager 15% yield after crystallization from a complex reaction mixture. Surprisingly, initial attempts to condense **8** with one equivalent of the less activated glyoxylic acid monohydrate in refluxing THF provided **9** in 20% yield.[16] Optimization studies were performed using 50% aqueous glyoxylic acid solutions (Scheme 4).

It was found that condensation of **8** with aqueous glyoxylic acid occurs readily at ambient temperature to provide **11** in high yield.[17] The latter rearranges to **9** in a refluxing mixture of water and THF. This reaction appears to be acid-catalyzed since it is accelerated in the presence of a small excess of glyoxylic acid. However, NMR studies indicated that decarboxylation of **11** to oxazolidine **12** is a serious side reaction at higher temperatures. Heating **12** with aqueous glyoxylic acid in THF also provided **9**, confirming that the acetal moiety is readily exchanged under the reaction conditions. These studies suggested that the low yields in our initial experiments were due to the partial decarboxylation of glyoxylic acid to formaldehyde via **11** and that better yields for **9** can be obtained by using an excess of glyoxylic acid.[18] Indeed, after heating a solution of **8** with an optimized 2.3 equivalents of aqueous glyoxylic acid in THF at reflux and an adjustment of the solvent composition from predominantly THF to predominantly water, compound **9** could be crystallized directly from the reaction mixture in 76% yield.

Scheme 5



Synthesis of *sec*-Phenethyl Alcohol 4. Several options for the synthesis of enantiomerically pure 3,5-bis(trifluoromethyl)-*sec*-phenethyl alcohol **4** were considered. The catalytic asymmetric (transfer) hydrogenation processes developed by Noyori and co-workers[19] were particularly appealing to us. A modification of the ruthenium catalyzed transfer hydrogenation using (1*S*, 2*R*)-*cis*-amino-2-indanol as the ligand[20] attracted our attention since this compound is readily available at Merck.[21] Commercially available ketone **13** could be reduced to (*R*)-**4** in 91% e.e. and 92% yield under these conditions (Scheme 5).

A slightly higher enantioselectivity was obtained after fully optimizing an oxazaborolidine-catalyzed borane reduction[22] of the ketone. Slow addition of **13** to a solution containing 2 mol % of the (*S*)-catalyst and 0.6 equiv of BH_3·$PhNEt_2$ complex in methyl *tert*-butyl ether between −10 and 0 °C yielded (*R*)-**4** in 97% yield and 93% e.e. (95% e.e. when 5 mol % of the catalyst was used). In either case, the enantiopurity of (*R*)-**4** could be conveniently upgraded to >99% e.e. via a recrystallization.

Synthesis of Lactam Acetal 16. The projected union of racemic **9** with enantiopure (*R*)-**4** to yield the desired (*R*,*R*)-**16** via a crystallization-induced diastereoselective transformation consists of several components: the activation of **9**, the substitution reaction of the resulting product with **4**, the equilibration of the expected products **16** and **17**, and the selective crystallization of **16** from the reaction mixture. Each of these components was first studied separately before they were brought together to act in concert.

Initially, lactol **9** was activated as an imidate.[23,24] Stirring **9** with an excess of trichloroacetonitrile and potassium carbonate in dichloromethane at ambient temperature cleanly yielded **14** (Scheme 6). Upon completion of the reaction the solids were filtered, and the filtrate was concentrated to dryness furnishing **14** as an unstable crystalline solid. This compound reacted instantaneously with **4** after addition of a catalytic amount of TMSOTf to yield a 55:45 mixture of diastereomers **16** and **17** in 90% yield. Although this protocol worked quite well on small scale, it proved difficult to scale.[25] Invariably, significant amounts of "dimeric" **18**[26] were also produced. Control experiments confirmed that **14** reacted faster with **9** than with **4**. In a

(15) (a) Le Rouzic-Bleevre, A. *Fr. C. R. Hebd. Seances Acad. Sci., Ser. C.* **1976**, *282*, 307−310. (b) Mancilla, T.; de Jesus Rosales, M.; Garcia-Baez, E. V.; Carrillo, L. *Heteroatom. Chem.* **1995**, *6*, 605−609.

(16) For another use of glyoxylic acid monohydrate in a direct condensation reaction: Woodward, R. B.; Gosteli, J.; Ernest, I.; Friary, R. J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, C.; Whitesell, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 6853−6855.

(17) (a) Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron* **1995**, *51*, 4043−4056. (b) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051−1053.

(18) It was demonstrated that disproportionation of glyoxylic acid into oxalic and glycolic acid does not occur under these reaction conditions.

(19) For a review: Noyori, R.; Ohkuma, T. *Ang. Chem., Int. Ed.* **2001**, *40*, 40−73.

(20) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226−5228.

(21) (a) Larrow, J. F.; Roberts, E.; Verhoeven, T. R.; Ryan, K. M.; Senanayake, C. H.; Reider, P. J.; Jacobsen, E. N. *Org. Synth.* **1999**, *76*, 46−56. (b) Gosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937−961.

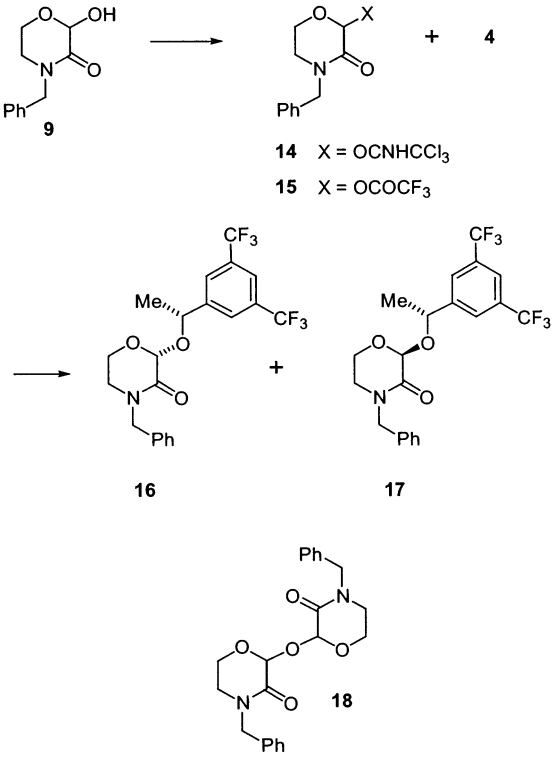
(22) (a) Corey, E.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926. (b) Review: Itsuno, S. *Org. React.* **1998**, *52*, 395−576.

(23) Schmidt, R. R.; Kinzy, W. In *Advances in Carbohydrate Chemistry and Biochemistry*; Horton, D., Ed.; Academic Press: San Diego, 1994; Vol. 50, pp 21−123.

(24) For reviews of activation methods in carbohydrate chemistry: (a) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(25) It takes significantly longer to remove dichloromethane and the excess trichloroacetonitrile via vacuum distillation on larger scale. When trichloroacetonitrile is removed slowly the imidate equilibrium shifts back to the starting materials.

Scheme 6



closely related procedure, **9** was reacted with trichloroacetonitrile in the presence of DBU in a mixture of toluene and heptane which led to the crystallization of **14** directly from the reaction mixture. Addition of the resulting **14** to a mixture of **4** and a catalytic amount of $BF_3{\cdot}Et_2O$ again gave a 55:45 mixture of **16** and **17** (95% yield). Even though the latter process proved scalable, the isolation and handling of the rather unstable and moisture sensitive **14** was still quite problematic. Consequently, the potential for alternative and less reactive activation of **9** was investigated. The glycosyl chloride and bromide (X = Cl, Br) could be prepared from **9** relatively easily under a variety of conditions but they proved to be rather unstable and gave **16** and **17** in lower overall yield than via the imidate. It was discovered that several esters of **9** provided sufficient activation for a reaction with **4** using $BF_3{\cdot}Et_2O$ catalysis.[27] The acetate of **9** significantly transesterified to **4** which obviously lowered the yield of the coupling reaction. Pivaloate, isobutyrate, and benzoate esters showed a reduced tendency for transesterification. However, overall yields for activation and coupling with **4** were substantially lower for these esters than for the imidate (80−85% vs 90−95%). Finally, it was found that the trifluoroacetate ester provided excellent activation with minimal transesterification. Moreover, **15** could be conveniently prepared in quantitative yield without the need for a base by simply adding 1.0 equiv of trifluoroacetic anhydride to **9**.[28] Reaction of freshly prepared **15** with **4** catalyzed by $BF_3{\cdot}Et_2O$ followed by a straightforward aqueous workup yielded the 55:45 mixture of **16** and **17** in 95−98% overall yield. This process proved the most practical and scalable.

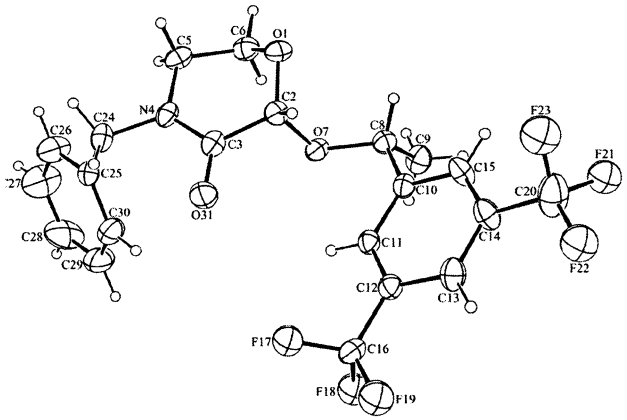


Figure 1. Perspective view (ORTEP) of **16**, showing crystallographic numbering scheme. Non-hydrogen atoms are represented by ellipsoids corresponding to 20% probability envelopes. Hydrogen atoms have been drawn at an arbitrary size.

Table 1. Equilibration of Lactam Acetal Diastereomers **16** and **17** under Basic Conditions

entry	conditions	result	final d.e. (%)
1	LDA, THF, −78 °C	decomposition[a]	
2	KO^{t}Bu, THF, −78 °C	decomposition[a]	
3	Et_3N, toluene, 100 °C[b]	no reaction	10
4	LiO^{t}Bu, ^{t}BuOH, 22 °C[c]	no reaction	10
5	KO^{t}Bu, ^{t}BuOH, 22 °C[d]	equilibration	30
6	TMG, ^{t}BuOH, 22 °C[e]	no reaction	10
7	^{t}Bu-P_4[34], ^{t}BuOH, 22 °C[f]	equilibration	30

[a] The starting materials were converted within minutes to a mixture of **19** and **20** and several other unidentified products upon addition to a 0.15 M solution of the base at −78 °C. [b] A 0.2 M solution of the starting materials in toluene with 2 equivalents of Et_3N was heated at 100 °C for 2 d. [c] A 0.25 M solution of the starting materials in a 9:1 mixture of hexanes/^{t}BuOH was stirred at ambient temperature with 0.5 equivalent of a 1.0 M LiO^{t}Bu/THF solution for 16 h. [d] A 0.2 M solution of the starting materials in hexanes was stirred at ambient temperature with 0.5 equivalent of a 1.0 M KO^{t}Bu/^{t}BuOH solution for 16 h. [e] A 0.2 M solution of the starting materials in a 4:1 mixture of hexanes/^{t}BuOH was stirred at ambient temperature with 1.0 equivalent of 1,1,3,3-tetramethylguanidine for 16 h. [f] A 0.25 M solution of the starting materials in a 9:1 mixture of hexanes/^{t}BuOH was stirred at ambient temperature with 0.5 equivalent of a 1.0 M ^{t}Bu-P_4/hexane solution for 16 h.

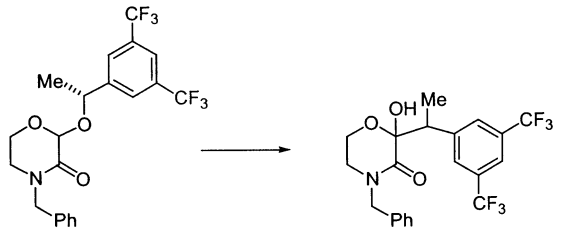
The surprisingly apolar diastereomers **16** and **17** were obtained in pure form via careful chromatography. Although the desired **16** was a highly crystalline compound (Figure 1), diastereomer **17** turned out to be a significantly lower melting solid. As hoped, seeding of a typical crude 55:45 mixture of **16** and **17**, respectively, with **16** led to selective crystallization of the desired component. Obviously, the efficiency of this process was rather low in the absence of equilibration between **16** and **17**. A variety of conditions was therefore probed to determine if equilibration between the diastereomers could be achieved. Under various Lewis or Brönsted acidic conditions, **16** and **17** did not interconvert. Screening of basic conditions was more successful (Table 1). Under the conditions of entries 5 and 7, equilibration could be discerned. In both cases, the ratio of **16** and **17** changed from the initial 55:45 to 65:35 at equilibrium.[29,30] However, the equilibration was accompanied by some

(26) This compound is a mixture of the *dl* and *meso* isomers in a statistical ratio according to HPLC.

(27) Reference 24b lists several precedents for this type of activation in carbohydrate chemistry. Similar reactivity was recently noted with related compounds: (a) Aoyagi, Y.; Jain, R. P.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3472−3477. (b) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 10 419−10 433. (c) Williams, R. M.; Colson, P.-J.; Zhai, W. *Tetrahedron Lett.* **1994**, *35*, 9371−9374.

(28) It is critical to add exactly 1.0 equivalent of TFAA to **9** to obtain the optimum yield. When the anhydride is undercharged with respect to **9** the yield for the overall process is lowered due to a reaction of **15** with the unconverted **9** to yield a mixture of isomeric **18** (meso and *d*/*l*). Conversely, when the anhydride is overcharged relative to **9** part of **4** is also esterified which also results in a lower overall yield for the coupling reaction.

Scheme 7



16/17 **19/20**

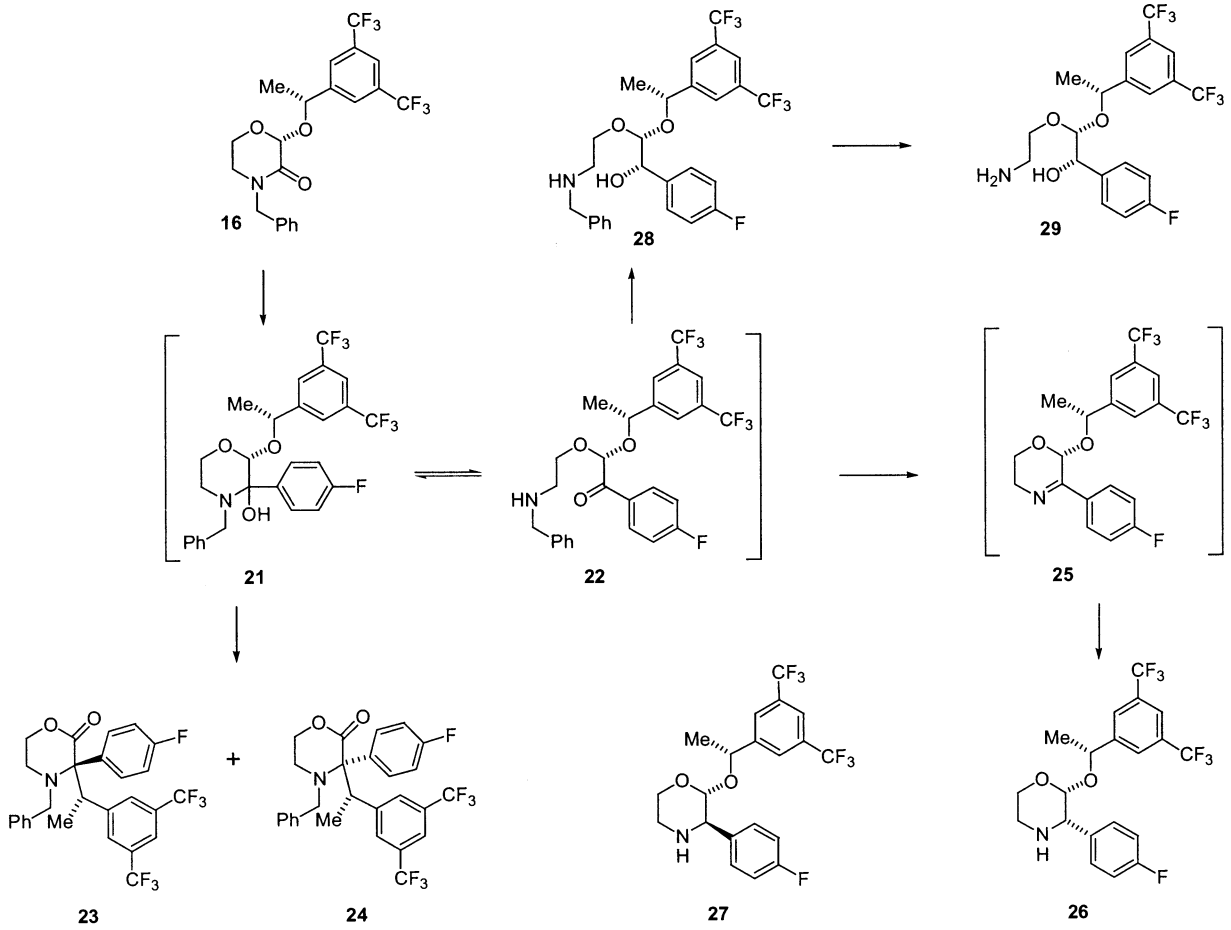
decomposition of **16** and **17**. The two most significant decomposition products (approximately 3:1 ratio according to HPLC analysis) proved identical to the two most abundant products generated under aprotic basic conditions (entries 1 and 2 of Table 1). Chromatographic purification provided a mixture of these components from which the major crystallized. Upon dissolution in $CDCl_3$, this major product slowly converted to the same mixture as before crystallization. The structures of these compounds were assigned as **19** and **20** (Scheme 7) on the basis of NMR experiments. Unfortunately, these experiments did not allow the assignment of the relative stereochemistry of the ketal and methyl bearing carbons for the major and minor isomer with complete confidence. It was established that both **19** and **20** were each a 86:14 mixture of enantiomers.[31] The structure and enantiopurity of these products strongly suggest that they are formed via an interesting [1,2]-Wittig rearrangement.[32,33]

The impact of the solvent polarity and the base on the equilibration and decomposition of **16** and **17** was further studied in a series of experiments which used a minimum amount of THF in the reaction medium in order to maintain homogeneity and prevent crystallization-induced effects. The rate of equilibration was significantly faster with potassium than with lithium *tert*-butoxide (~16 h vs >48 h for complete equilibration, respectively).[35] Equilibration was much slower with primary alkoxides (regardless of their counterion). Both observations are probably explained by the increase in basicity in going from primary to tertiary alkoxides and in going from lithium to potassium alkoxides.[36] During further optimization of the result in entry 5 (Table 1) it was found that the rate of equilibration increased with increasing amounts of potassium *tert*-butoxide. Unfortunately, the rate of the [1,2]-Wittig rearrangement also increased with more base, leading to the formation of significant amounts of **19**/**20** at ambient temperature. However, the rearrangement reaction can be nearly completely suppressed by maintaining the reaction temperature below 0 °C. Thus, aging a solution of **16** in *tert*-butyl alcohol with 5 equivs of 1.0 M KO^{t}Bu/THF at 20 and at 0 °C, respectively, yielded a 65:35 and a 78:22 mixture of **16** and **17** with 11 and <1 area% of **19**/**20**, respectively. Crystallization of **16** cannot be achieved in high yield from heptane solutions which contain even relatively small amounts of *tert*-butyl alcohol. Thus, it was necessary to identify a less polar proton donor with an appropiate pK_a to lower the solubility of **16** under the equilibration conditions. A survey of readily available lipophilic tertiary alcohols yielded 3,7-dimethyl-3-octanol (tetrahydrolinalool) as an attractive candidate.[37] Fortuitously, the equilibration rate was significantly faster in this alcohol than in *tert*-butyl alcohol with equilibrium achieved within 3 as compared to 20 h (2 equivs of a 1.0 M KO^{t}Bu in THF solution added to a 0.16 M solution of **16** in the respective alcohols at 20 °C). We speculate that the alkoxide anion is a stronger base in the less polar 3,7-dimethyl-3-octanol than in the more polar and better solvating *tert*-butyl alcohol.[38] Substituting THF in the above conditions with heptane and seeding with **16** then led to a practical process in which the desired diastereomer crystallizes with high recovery and the undesired diastereomer is continuously epimerized. Additional optimization studies showed that by replacing potassium *tert*-butoxide with the potassium salt of 3,7-dimethyl-3-octanol[39] the amounts of base and alcohol could be further reduced. Thus, in the optimum process the crude 55:45 mixture of **16** and **17** resulting from the glycosidation reaction is dissolved in heptane and 0.9 equiv of 3,7-dimethyl-3-octanol are added. The mixture is then cooled to between −10 and −5 °C.[40] After seeding with **16** and addition of 0.3 equiv of the potassium salt of 3,7-dimethyl-3-octanol, the crystallization-driven epimerization starts. After 5 h, the initial 55:45 mixture has been transformed into a 96:4 mixture (on a homogenized basis) from which **16** can be isolated in 83−85% overall yield (based on **4**).[41] The enantiopurity of **16** is >99% e.e. The above-described crystallization process is so powerful that starting with enantiomerically pure **4** is not critical. Using **4** of only 91% e.e. still provided >99% e.e. pure **16** under the above conditions, albeit with a slightly reduced overall isolated yield (76%; i.e., 80% when corrected for the enantiopurity of **4**).

Conversion of Oxazinone 16 to Morpholine 26. Several options for expedient conversion of *N*-benzyl lactam **16** to α-arylamine **26** were considered. The combination of a formal nucleophilic addition of a 4-fluorophenyl group and a reduction appeared the most straightforward. However, to the best of our knowledge there is no literature precedent for achieving this type of transformation in a relatively small number of steps. It was expected in the case at hand that the relatively bulky 2-alkoxy group in **16** would direct any reaction to the opposite face of the molecule. Thus, to obtain the desired stereochemistry it is essential that the nucleophilic addition precedes the

(29) As expected, results starting with a mixture of **16** and **17** or with either pure **16** or pure **17** were identical under these conditions.
(30) Several other N-alkyl analogues of **16**/**17** were prepared in order to determine the impact on the equilibrium ratio. Derivatives containing 4-phenylbenzyl, benzhydryl, and both enantiomers of α-methylbenzyl at the lactam nitrogen all equilibrated to an approximate 2:1 mixture of diastereomers upon subjection to the conditions of entry 5 of Table 1.
(31) In the absence of a reference compound, this HPLC method did not allow the assignment of the absolute structure of the major and minor enantiomers.
(32) (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann./Recueil* **1997**, 1275−1281. (b) Tomooka, K.; Kikuchi, M.; Igawa, K.; Keong, P.-H.; Nakai, T. *Tetrahedron Lett.* **1999**, *40*, 1917−1920.
(33) For a recent example of a similar reaction: Garbi, A.; Allain, L.; Chorki, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D.; Nakai, T.; Bégui, J.-P. *Org. Lett.* **2001**, *3*, 2529−2531.
(34) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167−1169. This base was purchased from Fluka.
(35) The performance with sodium *tert*-butoxide was very similar to that with potassium *tert*-butoxide.
(36) (a) Arnett, E. M.; Small, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 808−816. (b) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295−3299.
(37) Tetrahydrolinanool is available from Aldrich at approximately $100 for 500 mL. Only the racemic alcohol was used in our experiments. The effect, if any, of using enantiomerically pure solvent in this process has not been studied.
(38) Arnett, E. M.; Johnston, D. E.; Small, L. E. *J. Am. Chem. Soc.* **1975**, *97*, 5598−5600.
(39) The potassium salt of 3,7-dimethyl-3-octanol can be conveniently generated as a solution in heptane by adding potassium *tert*-butoxide to a solution of 3,7-dimethyl-3-octanol in heptane and distilling off *tert*-butyl alcohol.
(40) As expected on the basis of the melting point difference, compound **17** is considerably more soluble under these conditions than **16** (51 and 25 mg/mL, respectively).
(41) Interestingly, seeding with crystalline **17** leads to an identical endpoint providing additional evidence that **16** is the thermodynamic product in this process.

Scheme 8



reduction. Simultaneous deprotection of the *N*-benzyl group was another desired outcome of this process, as mentioned before.

In practice, it was not necessary to activate the lactam moiety toward nucleophilic addition. Lactam **16** reacted readily with 4-fluorophenylmagnesium bromide in a variety of solvents. The expected adduct **21** was obtained as a 2:1 mixture of diastereomers which are presumably in equilibrium via **22** (Scheme 8). The stereochemistry of the major and minor isomers could not be unequivocally established on the basis of their NMR spectra. In initial experiments, the Grignard addition reaction was worked-up and the resulting crude product mixture was hydrogenated in methanol using Pearlman's catalyst. Gratifyingly, the desired product was detected by HPLC as the main component in a complex mixture, and amine **26** could be crystallized as its 4-toluenesulfonic acid salt in 64% yield (based on **16**) from this mixture.

Some of the other reaction products were isolated from the mother liquors in two fractions via silica gel chromatography. The more polar fraction contained the amino alcohol **29**. The absolute carbinol stereochemistry in **29**, which presumably arises from **22** via **28**, was corroborated as (3*S*) via chemical correlation with trans morpholine derivative **27**.[42] The origin of this remarkable selectivity (the other carbinol epimer was not detected by HPLC analysis in the crude reaction mixture) is not clear. The less polar fraction of the chromatography contained two isomeric lactones in a 2:1 ratio according to HPLC and NMR analysis. The relative stereochemistry of both isomers was secured via single-crystal X-ray analysis[43] as **23** and **24**, respectively.[44] The rearrangement of the **21**/**22** mixture to give **23** and **24** can occur under remarkably mild conditions. For example, concentration of a solution containing **21** and **22** to dryness under high vacuum at ambient temperature led to complete conversion to **23** and **24**. Presumably, **21** and **22** can readily generate iminium intermediate **33** which upon proton loss converts to enamine **34**. The latter can then undergo a [1,3]-sigmatropic rearrangement (Scheme 9).[45,46]

Formation of **23** and **24** from **21**/**22** during the workup of the Grignard reaction and the hydrogenation obviously limited the efficiency of our first-generation process. Consequently, the isolation of the labile **21**/**22** was abandoned and a more robust one-pot process was developed. When the crude Grignard

(42) After reacting **29** consecutively with (1) FMOCCl, $NaHCO_3$; (2) MsCl, Et_3N; (3) Et_3N only **27** and none of **26** could be detected by HPLC. An authentic sample of *trans*-amine **27** was synthesized via chemistry described in ref 7.

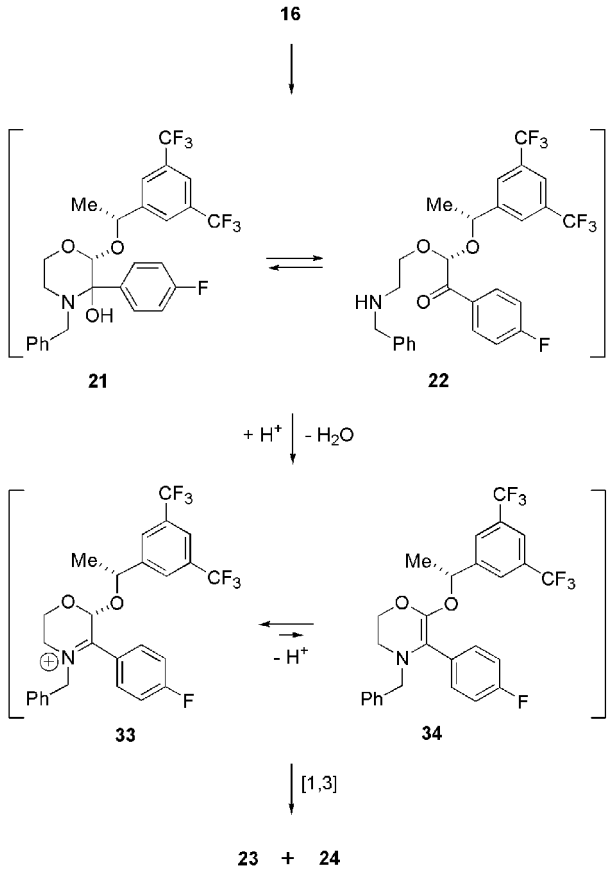
(43) The crystals of **23** used for this analysis were grown from the SiO_2-chromatographed material and shown to be a single enantiomer via chiral stationary phase chromatography. The crystals of **24** were grown from material purified after treating **21** with acid and these were racemic according to chiral stationary phase chromatography. Crystallographic details and ORTEP plots for each isomer are provided in the Supporting Information section.

(44) We were able to determine via chiral stationary phase chromatography that **23** and **24** were each >95% e.e. pure. However, at this point we cannot assign an absolute configuration for **23** and **24** with certainty. Thermal [1,3]-sigmatropic migrations occur with inversion of the migrating carbon; March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 1126.

(45) For related rearrangements: (a) Desmaele, D.; Champion, N. *Tetrahedron Lett.* **1992**, *33*, 4447−4450. (b) Bisel, P.; Lauktien, G.; Weckert, E.; Frahm, A. W. *Tetrahedron*: *Asymmetry* **1998**, *9*, 4027−4034 and references therein.

(46) The validity of the proposed mechanism is currently being studied.

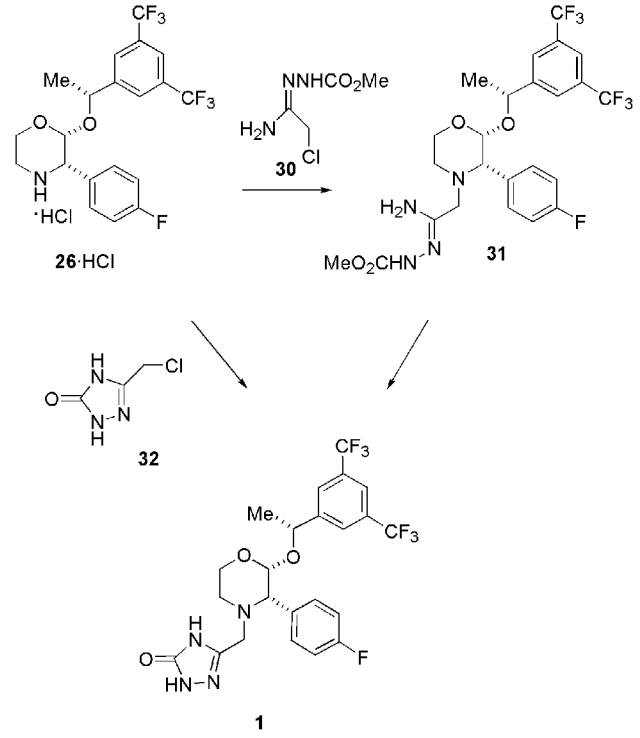
Scheme 9



mixture was quenched into methanol and then hydrogenated in the presence of a Pd/C catalyst a 1.7:1 mixture of **26** and **29**, respectively (area ratio by HPLC), was formed in a relatively slow reaction. The formation of **23** and **24** was insignificant under these conditions (<1%). In a key experiment, it was found that the hydrogenation selectivity in favor of the desired **26** increased dramatically when the quenched Grignard reaction mixture was acidified before the hydrogenation was performed. Additional studies showed that the nature and amount (i.e., relative to the amount of Grignard reagent) of the acid are critically important in achieving optimum reaction performance. A highly optimized protocol was eventually developed in which **16** was first allowed to react with 1.3 equivs of 4-fluorophenylmagnesium bromide in THF at ambient temperature. The resulting solution was then quenched with methanol and 1.8−2.2 equivs of 4-toluenesulfonic acid were added. Immediate hydrogenation at ambient temperature in the presence of 5% Pd/C yielded crude **26** in excellent yield. Kinetic studies of the hydrogenation reaction[47] showed that cyclic imine **25** is an important intermediate. The stereoselectivity in the reduction of **25** is typically >300:1. It is interesting to note that continued hydrogenation does not result in the reduction of any of the other benzylic bonds in **26**. Morpholine derivative **26** can be isolated from the reaction mixture as its hydrochloride salt in 91% overall yield (based on **16**), indicating that both the Grignard addition and the reduction occur in near quantitative yield. This process was successfully used to prepare multikilogram batches of **26**·HCl at a time.

(47) Details of these kinetic studies will be reported separately.

Scheme 10



Conversion of Morpholine 26 to Aprepitant (1). Conversion of **26**·HCl to Aprepitant is rather straightforward (Scheme 10). Alkylation of **26**·HCl in the presence of a base with chloro amidrazone **30**, which can be easily synthesized from chloroacetonitrile,[48] yields intermediate **31** in high yield. Thermolysis of the latter in toluene results in triazolinone formation and the desired **1** can be isolated in 85% overall yield. Alternatively, **26**·HCl can be alkylated with chloromethyltriazolinone **32** to afford **1** directly.[49]

Conclusions

The NK_1 receptor antagonist **1** was convergently synthesized in 55% overall yield over the longest linear sequence. A novel crystallization-induced diastereoselective glycosidation as well as an unprecedented stereoselective one-pot transformation of an 1,4-oxazin-3-one into a 3-(4-fluorophenyl)morpholine derivative serve as the foundation for this practical and exceedingly efficient approach. Furthermore, unexpected and interesting [1,2]-Wittig and [1,3]-sigmatropic rearrangements were also identified.

Acknowledgment. The authors thank Mr. Anthony Houck, Andrew Newell, and Charles Bazaral for their expert assistance in performing the hydrogenation reactions.

Supporting Information Available: Experimental details and spectral data for all compounds, X-ray crystallographic files for **16**, **23**, and **24** (CIF) and NMR spectra of **11**, **12**, **14**, **19**/**20**, **28**, and **29** (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

JA027458G

(48) Yanagisawa, I.; Hirata, Y.; Ishiii, Y. *J. Med. Chem.* **1984**, *27*, 849−857.
(49) Cowden, C. J.; Wilson, R. D.; Bishop, B. C.; Cottrell, I. F.; Davies, A. J.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 8661−8664.