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Synthesis of a Substance P Antagonist: An Efficient Synthesis of 5-Substituted-4-*N,N*-dimethylamino-1,2,3-triazoles

Michel Journet,* Dongwei Cai,* David L. Hughes, Jason J. Kowal, Robert D. Larsen,‡ and Paul J. Reider‡

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, RY800-B267, Rahway, New Jersey 07065-0900, U.S.A.

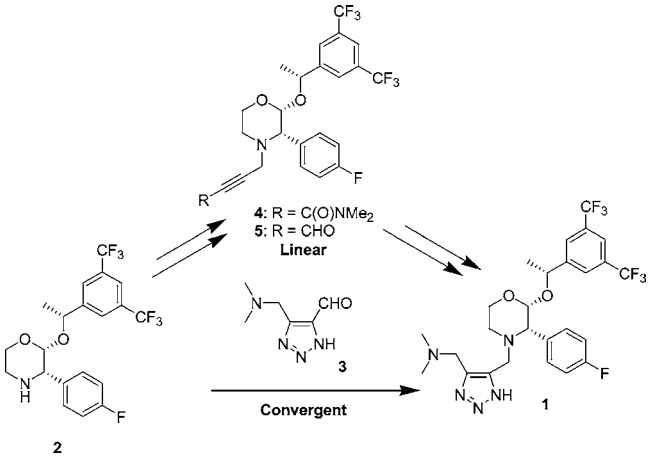
Abstract:

A highly efficient synthesis of the substance P antagonist 1 is reported starting from the optically pure morpholine acetal derivative 2. The 5-dimethylaminomethyl-1,2,3-triazole moiety is elaborated via a 1,3-dipolar cycloaddition between an activated acetylenic intermediate and sodium azide. Two approaches to the construction of the triazole moiety of 1 have been designed. The first approach is linear affording the side chain in four steps and 85−92% overall yield. The reactive acetylenic aldehyde 5 allowed for a mild azide cyclization. A simple reductive amination of the triazole aldehyde completed the synthesis of 1. An alternative, more efficient, convergent synthesis using analogous methodology developed from the linear synthesis was designed to improve the overall efficiency of the process as well as remove the concerns with the handling of azide. The triazole adduct was prepared offline in a two-step, one-pot operation as the building block 4-*N,N*-dimethylaminomethyl-1,2,3-triazole-aldehyde 3. Formylation of *N,N*-dimethylaminopropyne and azide cyclization were carried out as a through process to afford the triazole aldehyde 3 in 90% assay yield. The product was isolated in overall yields ranging from 67 to 81% depending on method. The aldehyde group of 3 was used for coupling to the morpholine building block through a reductive amination with $NaBH(OAc)_3$ in near quantitative yield to afford the substance P antagonist 1 as a hydrochloride salt in 95% yield from 2.

Introduction

Substance P is a peptide composed of 11 amino acids which binds to the neurokinin receptor (NK-1). Substance P (NK-1) receptor antagonists[1] have been shown to be potential therapeutic agents for a wide variety of important medical disorders. Among these was found a substance P antagonist that is effective in the treatment of chemotherapy-induced nausea and vomiting which led Merck to the identification of Aprepitant.[2] Heterocyclic-substituted methylmorpholine acetals have been identified as potent, orally bioavailable NK-1 receptor antagonists.[3,4] Substitution with a 5-dimethylaminomethyl-1,2,3-triazole[4] resulted in potent compound **1** as a water-soluble[3d] hydrochloride salt with desirable physical properties. Herein, we report two efficient syntheses of this substance P antagonist **1** starting from the optically pure morpholine derivative **2**[2] (Scheme 1). In both routes the triazole is produced through a 1,3-dipolar cycloaddition of an acetylenic aldehyde with sodium azide. In the first approach the dimethylaminomethyltriazole is constructed upon the morpholine in four linear steps,[5] whereas in the second it is prepared in two steps offline from

Scheme 1



* To whom correspondence should be addressed. E-mail: michel_journet@merck.com and dongwei_cai@merck.com.

‡ Current address: Amgen, One Amgen, Centre Dr., Thousand Oaks, CA 91320.

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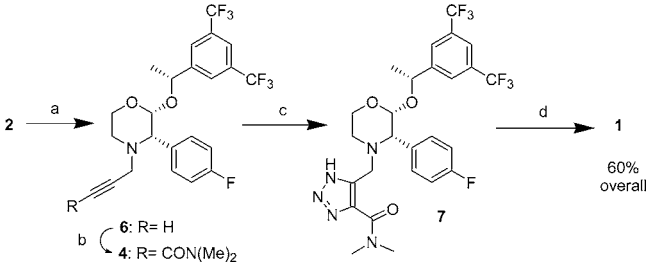
Scheme 2[a]

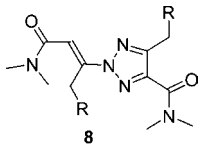


[a] Reagents and conditions: (a) Propargyl bromide, K_2CO_3, DMF, rt, 99%; (b) *n*-BuLi, −60 °C; Me_2NCOCl, THF, 85%; (c) NaN_3, AcOH, DMSO, 75 °C; (d) DIBAL-H, $PhCH_3$, 84% overall from **3**.

dimethylaminopropyne and coupled subsequently in a convergent manner.

Results and Discussion

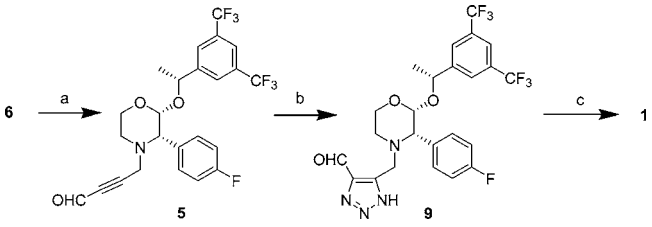
Linear Approach. The first-generation synthesis of **1** from **2** used a four-step sequence to incorporate the dimethylaminotriazole ring. Reaction of **2** with propargyl bromide in the presence of K_2CO_3/DMF gave rise to **6** in 99% yield. Deprotonation with butyllithium and addition of dimethylcarbamoyl chloride provided the propargylic amide **4**. The remainder of the synthesis presented some issues for future development. The sluggish azide cyclization of **4** to **7** required heating at 75 °C and 2 equiv of acetic acid to avoid the formation of the Michael-addition byproducts, such as **8**.



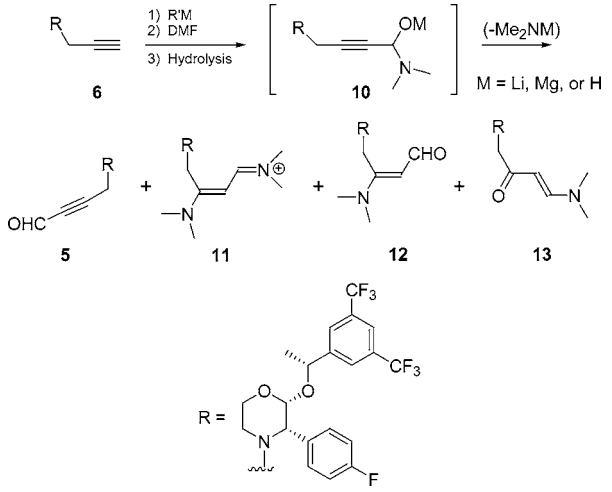
For the reduction of the amide to the dimethylamine of **1**, an inverse addition of the amide into a DIBAL-H solution was essential for achieving a high conversion. To separate the product in high recovery, a quench with saturated sodium potassium tartrate was necessary. This process to **1** was carried out in a moderate 60% overall isolated yield from the secondary amine **2** (Scheme 2).

A second-generation process[5] was designed to overcome the hazardous triazole formation and to increase the overall yield of the sequence (Scheme 3). The ease of an azide−alkyne cyclization to a triazole is governed by the polarization of the acetylene. This led us to consider alternative functional groups. Potentially, the intermediacy of the α,*β*-acetylenic aldehyde **5** could afford a more reactive system towards azide addition as well as providing a handle for

Scheme 3



Scheme 4



introduction of the dimethylamino group through reductive amination of the triazole aldehyde **9**.

The success of this new approach depended on the development of an efficient and scalable synthesis of the key intermediate **5**. No general, straightforward, high-yielding reactions were found in the literature for the preparation of α,*β*-acetylenic aldehydes from terminal alkynes. This was actually quite surprising since such alkynals have been widely used as Michael acceptors,[6] dienophiles in Diels−Alder reactions,[7] or as key intermediates in the synthesis of important natural products, such as cembranolide,[8a] calicheamicin,[8b] or neocarzinostatin.[9] A two-step procedure involving addition of paraformaldehyde followed by oxidation has been reported.[8,10b−c] In some isolated cases, formamide derivatives other than DMF have been applied, increasing the yields to 80−90%.[11]

As reported by Olah,[11b] the formylating reagent does not need to bear additional ligands to stabilize the intermediate α-aminoalkoxide making the cheap, readily available DMF a potentially convenient reagent. As a test of this concept, the alkyne **6** was treated with *n*-BuLi followed by the addition of DMF. In fact, the incipient intermediate aldehyde **10** (Scheme 4) was stable under the reaction conditions. However, the moderate yields in the direct formylation of the acetylide with DMF[9,10a,12] were due to the quench of **10**.

The source of the previously reported low yields has been related with the quench where side-reactions of the product

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(11) (a) For instance, using *N*-formylmorpholine, 3-phenylpropynal was synthesized from lithium phenyl acetylide in 80% yield: Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *J. Org. Chem.* **1984**, *49*, 3856−3857. (b) Olah, G. A.; Arvanaghi, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 878. (c) Comins, D.; Meyers, A. I. *Synthesis* **1978**, 403. (d) Amaratunga, W.; Fréchet, J. M. J. *Tetrahedron Lett.* **1983**, *24*, 1143−1146.
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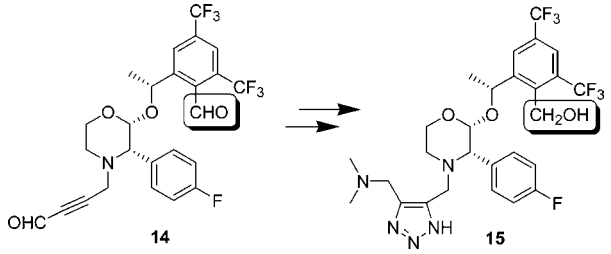
Scheme 5

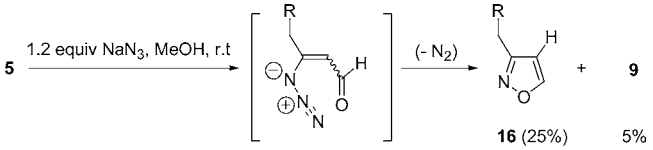


can predominate. In the quench the intermediate **10** collapses to release the strong nucleophile dimethylamine, which can subsequently react with the alkynal **5**. Three byproducts **11**−**13** were isolated from the formylation. Their formation depended on the way the reaction was hydrolyzed. In the quench with water, **5** was isolated in <50% yield, **12** being the major byproduct. In an acidic workup with aqueous acetic acid the stable iminium acetate **11** was formed, which was slowly hydrolyzed to the enaminoketone **13** upon aging. When harsher conditions were used (3 N HCl), crude ^{1}H NMR showed only the acetylenic aldehyde **5**, but the isolated yield was only 40−45%. In fact, reverse-phase HPLC analysis[13] of the aqueous layer revealed that the three Michael adducts **11**, **12**, and **13** had formed and partitioned into the aqueous layer as their hydrochloride salts. These three byproducts were eventually isolated and fully characterized by NMR to confirm their structure. Their formation was avoided through the inverse addition of the α-aminoalkoxide mixture into a buffered biphasic mixture of 10% aqueous monobasic potassium phosphate (4 equiv) and MTBE. Thereby, the product **5** was suitably stabilized from over-addition of the reaction components. The reaction itself proceeded in nearly quantitative yield. Because of the stablized α-aminoalkoxide intermediate and inverse quench, no over-addition from butyllithium was observed.

With this method, the terminal alkyne **6** was formylated under the optimized conditions to afford **5** in 97% assay yield with only 1 area % of the alkyne remaining. The iminium Michael adduct **11** was generated in only 0.25 area % (detected at $\lambda = 325$ nm) and was completely removed in the aqueous layer upon workup. The enamine **12** and ketoenamine **13** were generated in <0.1 area %.

A problem in this reaction was that only one equivalent of *n*-butyllithium could be tolerated; otherwise, even with a trace excess, abstraction of the aromatic proton adjacent to the trifluoromethyl group occurred to give the aldehyde byproduct **14**, which was converted into the hydroxymethyl derivative **15** in the final step of the process (Scheme 5).[14] The impurity **14** was generated in ~0.2 area % when an excess of 2−5 mol % of *n*-butyllithium was used. A stress reaction using 100 mol % excess of *n*-butyllithium resulted in the formation of 10 area % of the aldehyde **14** confirming that the impurity was generated from the overcharge of base. The eventual new process impurity **15** was poorly rejected upon crystallization of the HCl salt of **1**. To get a clean

Scheme 6



reaction, free of this undesired byproduct, a precise titration[15] and addition of *n*-butyllithium would be required.

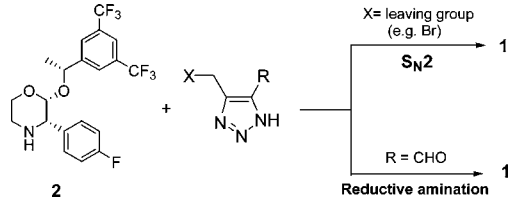
An alternative base was sought to avoid the over-deprotonation. Interestingly, even the bulky LDA generated 0.4 area % of the impurity with 15 mol % excess of base. Ethylmagnesium chloride proved to be the base of choice. The reaction could be run at room temperature. Even with a 20 mol % excess of the base, **14** was not detected.

Unfortunately, the workup needed to be re-designed. Previously, the phosphate buffer was used to prevent the generated dimethylamine from adding to the acetylenic aldehyde.[16] However, with the Grignard reagent, insoluble magnesium salts formed. Since the quench needed to be run at a pH between 4 and 6 to avoid the formation of the Michael adducts, several alternative buffers were screened. The monosodium salt of citric acid offered a buffer zone similar to that by KH_2PO_4. Since the substrate **6** was isolated as a toluene solution, this solution was used directly in the formylation. EtMgCl (1.2 equiv) was added at room temperature followed by addition of DMF (2 equiv). The reverse-quench of **10** into a biphasic solution of 7% aqueous sodium dihydrogen citrate (2 equiv, pH ≈ 3.9−4.5) and toluene produced two clear phases. Acetylenic aldehyde **5** was completely stable under these conditions and was synthesized in 99% yield. The only impurities were the remaining starting material **6** (0.35 area %) and the iminium Michael adduct **13** (0.25 area %), which was extracted into the aqueous layer.

Formation of **5** was so clean that the crude product was carried through to the triazole formation (Scheme 3) without purification. Fortuitously, the toluene solution of **5** could be used directly in the triazole formation after azeotropic distillation (KF < 250 μg water/mL) again obviating a solvent switch. The azide cyclization as in the original synthesis was best performed in DMSO. All attempts to run this reaction in another solvent met with failure. Interestingly, only 5% of the triazole aldehyde **9** was formed in methanol where the major impurity (25%) was the isoxazole **16** (Scheme 6; R same as in Scheme 4). This indicates that the 1,3-dipolar cycloaddition does not proceed by a concerted mechanism but more likely through a conjugate addition of the azide followed by cyclization. Unlike the acetylenic amide **4**, the cyclization of **5** occurred instantaneously and quantitatively in DMSO at room temperature to give the penultimate triazole aldehyde **9**. With the aldehyde, the reactivity was so high that acetic acid was unnecessary. This was a major accomplishment in that it avoided the potential generation of HN_3, a highly explosive gas.[17] As previously observed, good mixing was tremendously important in this

(13) All Michael adducts have a strong absorption at 325 nm.
(14) Under the conditions we used for the reductive amination of triazole aldehyde **9** with borane·dimethylamine, aldehyde **14** was reduced to the corresponding hydroxymethyl derivative **15**.
(15) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509−510.
(16) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427−6428.
(17) Stohlmeier, M.; Thewalt, K. *Chem. Ind. Dig.* **1993**, *6*, 124−128.

Scheme 7

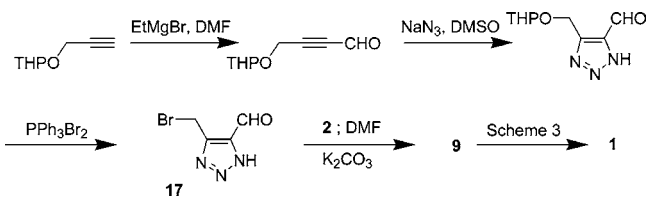


reaction since any starvation of azide during the addition led to some decomposition.[18] With this new procedure the triazole aldehyde **9** was prepared in 99% assay yield (Scheme 3).

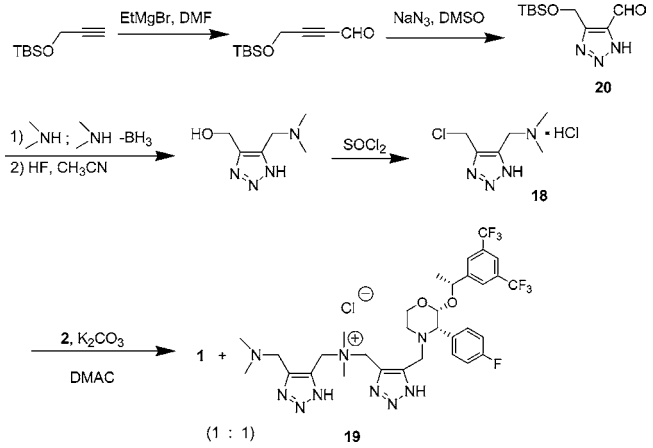
At this stage of the synthesis, the penultimate intermediate **9** had been synthesized in 97% assay yield starting from the secondary amine **2**. To develop a through process and obviate the workup between the reactions, the reductive amination was investigated in DMSO. Fortunately, DMSO was the best solvent for the reduction. Only ~0.1% alcohol byproduct was generated as compared to ~1% alcohol in other solvents, such as methanol, ethanol, 2-propanol, or THF. A 40 wt % aqueous solution of dimethylamine was the most convenient source of the amine. The readily available borane·dimethylamine complex proved to be a highly effective reducing agent. A more reactive borane·amine complex, such as borane·pyridine converted to borane·dimethylamine in situ, whereas a less reactive borane·amine, such as borane·triethylamine required forcing conditions. As a throughput process with no workup, 40 wt % aqueous dimethylamine was added to the DMSO/toluene mixture of **9**, followed with acetic acid and borane·dimethylamine. The reaction mixture was aged at 40 °C for 12−18 h, and the product **1** was generated in 98% assay yield (Scheme 3). The final product **1** was crystallized as the hydrochloride salt (4 N HCl in isopropyl alcohol) from toluene/heptane in 89% overall yield from **2**.

Convergent Approach. Although the linear process was very efficient and high yielding (89−92% overall), none of the intermediates was crystalline. This necessitated the development of a throughput process that, although efficient, lacked flexibility in the preparation of this compound. In addition there were concerns with running the triazole preparation with excess azide and the addition of acetic acid subsequently for the reductive amination. Rather than construct the triazole on the morpholine scaffold in a linear approach (Scheme 3), a process where the triazole was constructed offline and added directly in the last step would afford an efficient, convergent synthesis of **1** (Scheme 7).[19] Two approaches for coupling a triazole building block to **3** were considered. A logical strategy could employ a direct alkylation of the secondary amine **3** with a halomethyl-1,2,3-triazole. In contrast, a triazole carboxaldehyde derivative

Scheme 8



Scheme 9



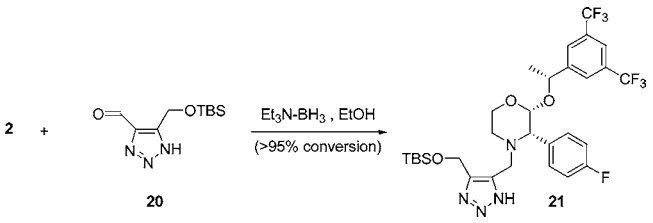
could be used in a reductive amination. Both approaches were considered as is disclosed herein.

In the alkylation approach the bromomethyl triazole **17** was prepared easily from THP-protected propargyl alcohol (Scheme 8).[20] Alkylation of the morpholine **2** effectively intercepted the synthesis of **1** at compound **9** (Scheme 3). An attempt to design a more convergent route through the synthesis of **18** did indeed give **1** in one step from **2**, but the over-alkylation to **19** could not be controlled (Scheme 9).

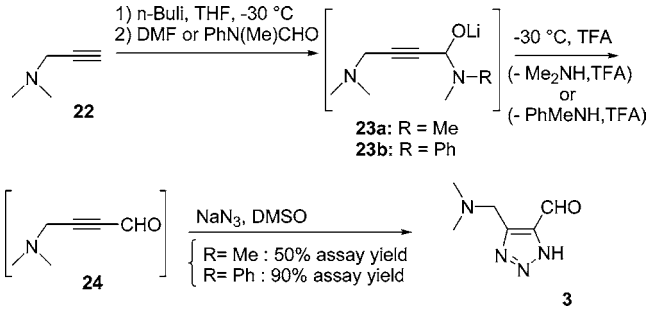
The reductive amination approach to **1** was tested with the aldehyde **20** as prepared in Scheme 9. To our delight, the reductive amination of **2** with **20** using borane·triethylamine as the reducing agent in ethanol gave the coupled product **21** in 95% conversion (Scheme 10). With the feasibility of this approach confirmed, the synthesis of the optimal coupling intermediate **3** was designed. Since the developed synthesis of the dimethylaminomethyltriazole group of **1** was incredibly efficient and high-yielding, a similar strategy to the preparation **9** (Scheme 3) was followed through formylation of *N*,*N*-dimethylaminopropyne (**22**) and 1,3-dipolar cycloaddition of the alkyne with sodium azide (Scheme 11).

Commercially available 1-(dimethylamino)-2-propyne (**22**) was chosen as the starting material (Scheme 11). The substrate was deprotonated and formylated as previously developed. Due to the greater water solubility of the dimethylamino-substituted intermediates, as opposed to the protected propargyl alcohols in Schemes 8 and 9, the workup became a challenge. Moreover the aldehyde **24** was unstable above −30 °C even under anhydrous conditions due to polymerization and could only survive this temperature for a couple of hours. As a result, the biphasic quench with aqueous sodium dihydrogen citrate/toluene and the stepwise sequence developed in the linear process for **1** could not be used.

Scheme 10



Scheme 11

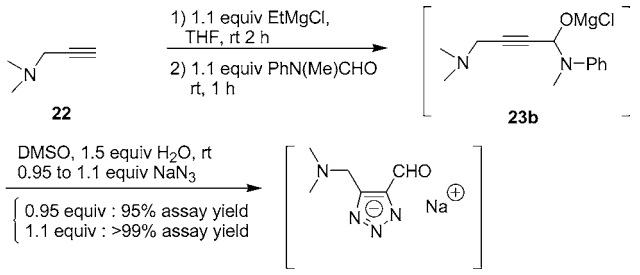


Deprotonation of the alkyne **22** was initially achieved with *n*-BuLi. The isolation of **24** was not possible due to its instability, requiring the quench and age to be carried out at low temperatures. The intermediate lithium alkoxide **23** was hydrolyzed with anhydrous TFA at −30 °C ,and the resulting acetylenic aldehyde **24** was added into a DMSO solution of sodium azide at room temperature to give **3** in a moderate 50% assay yield. Some byproducts were identified as Michael adducts resulting from the addition of dimethylamine onto the very reactive electrophile **24**, as observed by us previously.[16] Perhaps a less nucleophilic amine could be generated by changing the formylating reagent. Indeed, *N*-methylformanilide, generating the less reactive byproduct *N*-methylaniline, increased the assay yield to 90% reproducibly.

To overcome the special handling required with the reactive intermediate **24** the direct quench of **23b** into sodium azide was investigated. In our study of the synthesis of variously substituted acetylenic aldehydes,[20] the magnesium or lithium alkoxide intermediates proved to be stable at room temperature for at least 24 h under anhydrous conditions. This was also true in the case of the formylation of 1-(dimethylamino)-2-propyne. However, a fast hydrolysis occurred upon addition of water to give the corresponding aldehyde **24**, which polymerized readily to give black tars. On the basis of these simple observations, we were confident that the stable magnesium aminoalkoxide intermediate **23b** could be added into a wet DMSO solution of sodium azide to give the triazole aldehyde **3** directly (Scheme 12). 1-Dimethylamino-2-propyne was deprotonated at room temperature with 1.1 equiv of ethylmagnesium chloride in THF and was reacted with 1.2 equiv of *N*-methylformanilide. The resulting magnesium aminoalkoxide **23b** was aged at room temperature for an hour and added at room temperature into a vigorously stirred 0.5 M DMSO solution of 1.1 equiv of sodium azide containing 1.5 equiv of water. Good mixing was tremendously important since any starvation of azide led to partial decomposition of the liberated **24**. This throughput process using only two vessels afforded the triazole aldehyde in quantitative assay yield.

At the end of the reaction there was still an excess of sodium azide remaining. To address the safety concerns in quenching the reaction mixture with an acid the residual azide

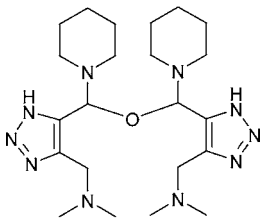
Scheme 12



had to be avoided. Therefore, the process was conducted with 0.95 equiv of sodium azide affording **3** in 90% assay yield from dimethylaminopropyne (95% from azide). This yield penalty was to be expected since with a deficit of azide the unreacted **24** polymerizes. An acceptable level of residual sodium azide was reached, which was assayed at ≤30 ppm.[21] Although a quantitative assay yield of **3** could be obtained with 1.0 equiv of azide, while maintaining the azide level at <30 ppm at the end of the reaction, the greater safety margin with 0.95 equiv was preferable.

The high water solubility of **3** required changes in the generic process to 4-substituted-1,2,3-triazole-5-carboxaldehyes.[22] A direct extraction out of the reaction media was not feasible with the presence of DMSO. Replacement of DMSO was not an option since the cyclization with sodium azide only proceeded well in this solvent. The preparation of derivatives of the triazole, such as benzyl or trimethylsilyl, through cyclization with alternative azide reagents failed. Precipitation of an insoluble salt, such as calcium or barium, or the formation of an insoluble bisulfite adduct[23] was also unsuccessful. Three different isolation processes were eventually developed to give **3** as a crystalline compound ranging in 67−81% overall isolated yield from **22**. Ion exchange chromatography using Dowex resins gave the best recovery (81% overall yield) and was used to prepare 5 kg of the triazole aldehyde. However, the large volumes of solvent made this isolation unsuitable for a long-term process of the drug.

Interestingly, we found that the piperidine adduct **25** could be crystallized directly from the reaction mixture (DMSO).

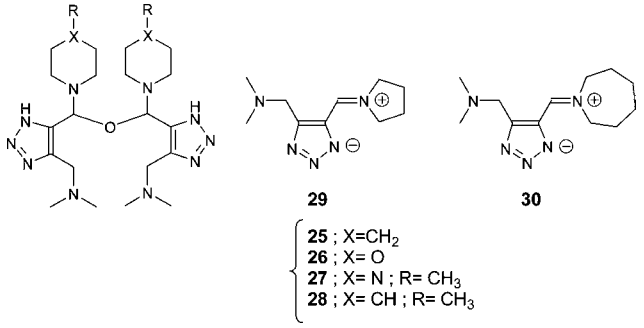


25

Depending on the size of the ring, the resulting adduct had two different structures (Scheme 13). Cyclic secondary

(18) In the absence of sodium azide, the anion of triazole aldehyde **8** may react with acetylenic aldehyde **4** as observed with **7**.
(19) Cai, D.; Journet, M.; Kowal, J.; Larsen, R. D. U.S. Patent 6,051,717, 2000.
(20) Journet, M.; Cai, D.; Kowal, J. J.; Larsen, R. D. *Tetrahedron Lett.* **2001**, *42*, 9117−9117.
(21) Sodium azide was assayed by reverse phase HPLC using a C-18 Metachem inertsil ODS-3 column (250 mm × 4.6 mm, 5 μm) with a flow rate of 0.75 mL/min and using UV detection at 200 nm. Elution was a gradient using a 10/90 mixture of acetonitrile/water (0.1% H_3PO_4) to 30/70 in 20 min. Retention time for azide was 7.35 min.
(22) Triazole aldehyde **3** is highly water soluble. Its solubility is 63 g/L in methanol and DMSO, 19 g/L in DMF and <4 g/L in 2-propanol, 2-butanol, chloroform, THF, and toluene.
(23) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 1228−1235.

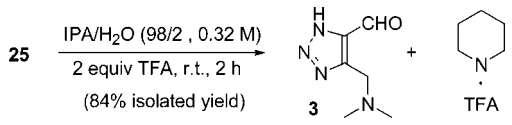
Scheme 13



amines other than a six-membered ring gave imminium adducts. However, when **3** was reacted with piperidine, a white crystalline product was produced in high recovery (75% isolated yield) with a good purity. It turned out that in this case the imminium was not observed but formation of the dimer adduct **25** occurred instead. The difference of solubility in DMSO of all of these adducts was huge: **25** was essentially insoluble (1 g/L) versus 58 and 35 g/L for the imminium·pyrrolidine adduct **29** and hexamethylene·imine adduct **30**, respectively. Other six-membered ring secondary amines were tested, and all of them gave a dimer adduct **26**−**28**.

The next step was the cleavage of **25** into **3** that could be achieved under acidic conditions in the presence of at least 0.5 equiv of water. The solvent of choice for this transformation was a 98/2 mixture of 2-propanol/water (7 mL/g). Several acids were tried. Acetic acid was inefficient, whereas the use of 2 equiv of TFA (Scheme 14) or methanesulfonic acid or trichloroacetic acetic acid all led to the crystallized heterocycle in 84% isolated yield. TFA was the best choice since ^{1}H NMR showed a very clean product with no contamination whatsoever of piperidine. Indeed, piperidine byproduct was completely removed as the TFA salt in the mother liquors, whereas trichloroacetic acetic led to a substantial amount of piperidine in the final isolated material. An isolated yield of 84% was the maximun we could get since the solubility of pure **3** in a 98/2 mixture of 2-propanol/water (10 mL/g) in the presence of one equiv of TFA salt of piperidine was 16 g/L.

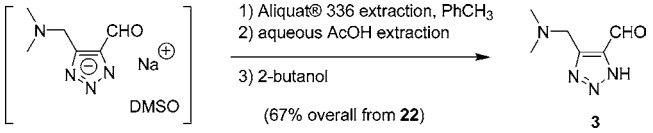
Scheme 14



The preferred isolation process utilized a reverse extraction of the sodium salt of **3** into toluene with Aliquat 336 (Scheme 15). The triazole was then extracted into aqueous acetic acid. Removal of the water and acetic acid by evaporative displacement with 2-butanol gave crystalline triazole aldehyde **3** in 67% overall yield.

The convergent synthesis was completed by reductive amination of **2** with **3**. As before borane·triethylamine was tested as the reducing agent in a solvent mixture of 2-propanol/DMSO containing acetic acid. Although the desired product **1** was obtained, the reaction was not clean.

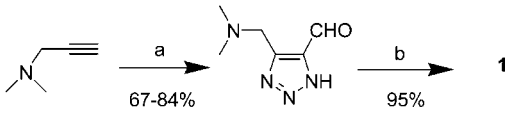
Scheme 15



In 2-propanol with 1 equiv of acetic acid the reaction gave a 92% assay yield with ∼95 area % purity. Many of these impurities were stable borane complexes, in particular, the borane complex with the dimethylamine moiety. To overcome the formation of these borane·amine complexes, sodium triacetoxyborohydride (STAB) was tested.[24] Acetic acid was not needed with STAB. In alcohol solvents the conversion was not good. THF worked quite well, but 2 equiv of aldehyde was needed to drive the reaction to completion due to the limited solubility of **3** in this system. Although DMSO was a suitable medium for the reductive amination, the reaction intermediates were not soluble, forming a gummy precipitate. In DMF the reaction worked very well with >99% conversion even with 1.1 equiv of **3**.

When the secondary amine *p*-toluenesulfonic acid salt was treated with STAB in DMF, the *N*-formyl analogue of **2** was generated at ∼0.1%/h at room temperature. Without STAB, no formylation occurred. STAB or some impurities in the STAB catalyzed this formylation with DMF which was eventually replaced with the more stable *N*,*N*-dimethylacetamide (DMAC). With DMAC no corresponding acetylation of the secondary amine occurred, and the reductive amination performed essentially the same as in DMF. With DMAC as solvent, the reaction performed perfectly in quantitative assay yield, generating product of >99% purity with only 0.1% of the secondary amine **2** remaining. This reaction was demonstrated on 4.4 mol scale in 95% isolated yield (99.6% reaction yield). Overall the process from the triazole aldehyde, prepared as throughput process from dimethylaminopropyne, was highly effective for preparing **1** (Scheme 16).

Scheme 16[a]



[a] Reagents and conditions: (a) (i) EtMgCl, THF, rt; (ii) PhN(Me)CHO, rt; (iii) NaN_3, DMSO, rt; (b) **2**, $NaBH(OAc)_3$, DMAC, 0−5 ° C.

Conclusion

Two processes for the synthesis of **1** have been developed. An efficient four-step linear process to prepare the substance P antagonist in 85−92% overall yield from the key intermediate **2** has been described. This process has been fully demonstrated with the preparation of kilogram quantities of **1**. To further improve upon the chemistry developed for the construction of the dimethylaminomethyltriazole a modification of the process was carried out offline to afford a convergent approach to **1**. A practical synthesis and isolation of triazole aldehyde **2** has been developed. A reductive amination strategy to join the triazole aldehyde **3** and the

secondary amine **2** using sodium triacetoxyborohydride afforded a high yielding, efficient preparation of the substance P antagonist in >95% yield.

Experimental Section

General. Reactions were performed under a positive atmosphere of dry nitrogen. Prior to use, the solvents were dried over 4 Å molecular sieves to <100 μg H_2O/mL. Water content was determined by Karl Fisher titration (KF). Commercially available reagents were purchased from Aldrich Chemical Co. and used as received. Melting points are uncorrected. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ.

2-(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-propargylmorpholine (6). To a stirred solution of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine *p*-toluenesulfonate salt (**2**) (609.0 g, 1.0 mol) in DMF (3.4 L) was added powdered potassium carbonate 325 mesh (346.0 g, 2.5 mol) at room temperature in one portion followed by the addition of propargyl bromide (80 wt % in toluene, 134.0 mL, 1.2 mol) over 5 min. The reaction was sligthly exothermic reaching ~29 °C. The reaction mixture was stirred at room temperature for 3.5 h (>99.9% conversion) and aqueous dimethylamine (40 wt %, 38.0 mL, 0.30 mol) was added in one portion and aged 0.5 h to convert the excess of propargyl bromide into the less toxic and water soluble 1-(dimethylamino)-2-propyne. The reaction mixture was diluted with toluene (6.7 L) and water (5.4 L), and the layers were separated. The organic layer was washed with water (2 × 3.4 L) and was finally concentrated under reduced pressure to give **6** as a yellow oil (470.5 g assay) in 99% yield, which was used as is in the next step. A standard as an oil was purified by flash chromatography on silica gel eluting with an 85:15 mixture of hexane/ethyl acetate (R_f 0.3). $[\alpha]_D^{25}$ +178 (*c* 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1 H), 7.39 (br t, J = 6.4 Hz, 2 H), 7.17 (s, 2 H), 7.04 (t, J = 8.8 Hz, 2 H), 4.90 (q, J = 6.6 Hz, 1 H), 4.33 (d, J = 2.8 Hz, 2 H), 3.71 (ddd, J = 11.4, 3.2, and 1.6 Hz, 1 H), 3.62 (d, J = 3.2 Hz, 1 H), 3.26 (d, J = 2.7 Hz, 2 H), 2.98 (td, J = 11.4 and 3.2 Hz, 1 H), 2.79−2.87 (m, 1 H), 2.20 (t, J = 2.7 Hz, 1H), 1.46 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J = 247.2 Hz, Csp^2−F), 145.5, 131.6 (q, J = 33.3 Hz, Csp^2−CF_3), 131.0 (d, J = 8.1 Hz), 126.3, 123.0 (q, J = 273.0 Hz, CF_3), 121.4, 115.1 (d, J = 21.1 Hz), 95.6, 74.3, 72.4, 66.4, 59.2, 51.0, 43.8, 24.4. Anal. Calcd for $C_{23}H_{20}F_7NO_2$ (475.40) C, 58.11; H, 4.24; N, 2.95. Found: C, 57.99; H, 4.21; N, 2.84.

(24) With various lots of purchased STAB two impurities were detected and identified as borane complexes of **1** previously observed with borane reducing agents. The STAB was contaminated with $NaBH_4$ as confirmed with solid-state boron-11 NMR study. Solution assays did not detect $NaBH_4$ due to the rapid reaction with STAB generating sodium mono- and bis-acetoxyborohydride. STAB was originally charged as a solid. By predissolving the reagent in DMAC the $NaBH_4$ contaminant was converted to the mixed forms of acetoxyborohydrides. As a result the borane byproducts were no longer observed. As an alternative STAB can be prepared in situ. $NaBH_4$ is very soluble in DMAC. Upon mixing with excess acetic acid STAB can be cleanly generated. Although adding either mixture to the other will generate the same quality STAB, addition of a solution of $NaBH_4$ into a cold (0 °C) solution of acetic acid (3.3 equiv) in DMAC will control the foaming caused by the release of hydrogen gas.

2-(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-4-(4-oxo-but-2-ynyl-(4-fluorophenyl))morpholine (5). To a stirred solution of crude 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-propargylmorpholine (**6**) (470.5 g assay, 0.99 mol) in dry toluene (3.4 L) was added ethylmagnesium chloride (2.0 M/THF, 595.0 mL, 1.19 mol) over 20 min, maintaining the temperature between 15 and 25 °C. The resulting solution was stirred for 2 h at room temperature, and anhydrous DMF (KF ≤ 100 μg H_2O/mL, 153.0 mL, 1.98 mol) was added over 10 min, maintaining the temperature between 20 and 25 °C. The solution was aged for an additional hour and was reverse added into a vigorously stirred biphasic solution prepared from sodium dihydrogen citrate (424.0 g, 1.98 mol) in water (5.6 L, ~7 wt %) and toluene (5.6 L) at room temperature (final pH~3.9 to 4.2). The biphasic reaction mixture was vigorously stirred for 4 h at room temperature, and the layers were separated. The organic layer was washed with water (2 × 4.0 L) and was concentrated under reduced pressure to give **5** as a yellow oil (493.5 g assay) in 99% yield, which was used as is in the next step. A standard was purified as an oil by flash chromatography on silica gel eluting with a 80:20 mixture of hexane/ethyl acetate (R_f 0.3). $[\alpha]_D^{25}$ +225 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3CN) δ 9.15 (s, 1 H), 7.75 (s, 1 H), 7.41 (br t, J = 6.8 Hz, 2 H), 7.33 (s, 2 H), 7.05 (t, J = 8.6 Hz, 2 H), 4.89 (q, J = 6.6 Hz, 1 H), 4.37 (d, J = 2.8 Hz, 1 H), 4.26 (td, J = 11.5 and 2.8 Hz, 1 H), 3.67 (ddd, J = 11.4, 3.2, and 1.6 Hz, 1 H), 3.59 (d, J = 2.8 Hz, 1 H), 3.42 (AB q, J = 20.0 Hz, 2 H), 2.89−2.94 (m, 1 H), 2.81 (td, J = 11.5 and 3.5 Hz, 1 H), 1.43 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3CN) δ 177.4, 162.5 (d, J = 244.3 Hz, Csp^2−F), 146.3, 132.5, 131.4, 130.9 (q, J = 33.1 Hz, Csp^2−CF_3), 126.8, 123.4 (q, J = 272.1 Hz, CF_3), 121.3, 114.8 (d, J = 24.6 Hz), 95.5, 90.6, 85.9, 72.2, 66.5, 58.9, 51.2, 43.6, 23.4. Anal. Calcd for $C_{24}H_{20}F_7NO_3$ (503.41) C, 57.26; H, 4.00; N, 2.78. Found: C, 57.45; H, 4.05; N, 2.56.

2-(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-oxomethyl-1,2,3-triazol-4-yl)methyl-3-(*S*)-(4-fluorophenyl)morpholine (9). To a vigorously stirred solution of sodium azide (76.1 g, 1.17 mol) in DMSO (3.1 L) was added a toluene (1.4 L) solution of crude 2-(*R*)-(1-(*R*)-(3,5-bis-(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-4-(4-oxo-but-2-ynyl-(4-fluorophenyl))morpholine (**5**) (493.5 g, 0.98 mol) over 20 min, maintaining the temperature between 20 and 25 °C. The resulting reaction mixture was stirred at room temperature for 0.5 h to give the triazole aldehyde derivative **9** (530.0 g assay) in 99% yield. No workup was performed; rather, the whole DMSO crude solution was carried through to the next step as is. A standard was purified as a foamy solid by flash chromatography on silica gel eluting with a 40:60 mixture of hexane/ethyl acetate (R_f 0.3). $[\alpha]_D^{25}$ +100 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3CN) δ 10.02 (s, 1 H), 7.75 (s, 1 H), 7.48 (br t, J = 7.8 Hz, 2 H), 7.32 (s, 2 H), 7.03 (t, J = 8.9 Hz, 2 H), 4.89 (q, J = 6.6 Hz, 1 H), 4.37 (d, J = 2.9 Hz, 1 H), 4.23 (br t, J = 11.8 Hz, 1 H), 3.83 (d, J = 15.3 Hz, 1 H), 3.58 (ddd, J = 11.5, 3.2, and 1.6 Hz, 1 H), 3.54 (d, J = 2.8 Hz, 1 H), 3.53 (d, J = 15.3 Hz, 1 H), 2.83 (br d, J = 11.6 Hz, 1 H), 2.51 (td, J = 11.8 and 3.5 Hz, 1 H), 1.43 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3-

CN) δ 185.3, 162.5 (d, $J = 244.0$ Hz, Csp^2−F), 146.3, 143.1, 133.3, 131.4, 131.2, 130.9 (q, $J = 33.1$ Hz, Csp^2−CF_3), 126.8, 123.4 (q, $J = 272.0$ Hz, CF_3), 121.2, 114.7 (d, $J = 21.6$ Hz), 95.6, 72.2, 68.8, 59.1, 52.4, 48.3, 23.5. Anal. Calcd for $C_{24}H_{21}F_7N_4O_3$ (546.44) C, 52.75; H, 3.87; N, 10.25. Found: C, 52.85; H, 3.83; N, 10.01.

2-(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(*S*)-(4-fluorophenyl)morpholine Hydrochloride Salt (1). To the crude DMSO reaction solution of 2-(*R*)-(1-(*R*)-(3,5-bis-(trifluoromethyl)phenyl)ethoxy)-4-(5-oxomethyl-1,2,3-triazol-4-yl)methyl-3-(*S*)-(4-fluorophenyl)morpholine (**9**) was added dimethylamine (40 wt % aqueous; 1.62 L), followed by 2-propanol (1.38 L) and acetic acid (0.55 L) while maintaining the temperature at <40 °C. Borane·dimethylamine complex (59.0 g; 0.97 mol) was added in one portion, and the reaction mixture was heated to 40 °C and aged for 16 h with stirring. The reaction was cooled to room temperature, diluted with water (1.5 L), and neutralized with concentrated phosphoric acid (~85%) to pH ≈ 8.5−9. The reaction mixture was further diluted with water (4.5 L) and toluene (6.0 L). The layers were separated, and the organic was washed with water (2 × 3.0 L) and concentrated under reduced pressure to give **1** as a yellow oil (541.5 g assay) in 97% yield as the free base. The crude oil was dissolved in toluene (2.2 L), and anhydrous hydrogen chloride (4.5 N in 2-propanol, ca. 209 mL, 0.94 mol) was added over 5 min at room temperature. *n*-Heptane (550 mL) was added in one portion. The mixture was seeded and aged for 2 h at room temperature. The remaining *n*-heptane (7.2 L) was added slowly over 2 h, and the resulting slurry was further aged for an additional 2 h at room temperature. The solids were filtered, washed with a 3:1 mixture of *n*-heptane/toluene (1.5 L), and dried at 40 °C under vacuum with a nitrogen stream to afford the pure hydrochloride salt of **1** (546.5 g) in 95% yield as a white solid. The overall isolated yield for the entire process was 89%. $[\alpha]_D^{25}$ +163 (*c* 1.0, MeOH): mp 201−202 °C (ethyl acetate/isopropyl alcohol/heptane). ^{1}H NMR (400 MHz, CD_3CN) δ 7.75 (s, 1 H), 7.54 (br t, $J = 6.4$ Hz, 2 H), 7.38 (s, 2 H), 7.11 (t, $J = 8.8$ Hz, 2 H), 4.90 (q, $J = 6.6$ Hz, 1 H), 4.34 (d, $J = 2.8$ Hz, 1 H), 4.21 (d, $J = 14.1$ Hz, 1 H), 4.15 (d, $J = 14.1$ Hz, 1 H), 4.10 (td, $J = 11.4$ and 2.4 Hz, 1 H), 3.69 (d, $J = 13.9$ Hz, 1 H), 3.56 (ddd, $J = 11.4$, 3.2, and 1.6 Hz, 1 H), 3.48 (br m, 1 H), 3.23 (d, $J = 13.9$ Hz, 1 H), 2.78 (s, 6 H), 2.74 (od, 1 H), 2.44 (br t, $J = 12.0$ Hz, 1 H), 1.44 (d, $J = 6.4$ Hz, 3 H);^{13}C NMR (100 MHz, CD_3CN) δ 163.5 (d, $J = 244.0$ Hz, Csp^2−F), 147.2, 142.3, 135.4, 134.1, 132.7 (d, $J = 8.0$ Hz), 131.9 (q, $J = 32.9$ Hz, Csp^2−CF_3), 127.9, 124.4 (q, $J = 271.5$ Hz, CF_3), 122.3, 116.0 (d, $J = 21.7$ Hz), 96.3, 73.1, 70.2, 60.1, 58.2, 53.0, 50.7, 49.4, 42.9, 24.5. Anal. Calcd for $C_{26}H_{29}ClF_7N_5O_2$ (611.98) C, 51.03; H, 4.78; N, 11.44. Found: C, 51.11; H, 4.67; N, 11.33.

4-*N*,*N*-Dimethylaminomethyl-5-formyl-1,2,3-triazole (3). A solution of 1-*N*,*N*-(dimethylamino)-2-propyne (83.5 g, 1.0 mol) in THF (460 mL) was cooled to 0−5 °C, and ethylmagnesium chloride (2.0 M, 550.0 mL, 1.1 mol) was added over 20 min while maintaining the temperature between 20 and 25 °C. The cold bath was removed, and the reaction mixture was aged at room temperature for 2 h. *N*-Methylformanilide (162.5 g, 148.0 mL, 1.2 mol) was added over 15 min at 20−25 °C. The reaction mixture was stirred at room temperature for an additional hour and was then added over 30 min into a vigorously stirred DMSO solution (2.0 L) containing sodium azide (61.8 g, 0.95 mol) and water (27.0 mL, 1.5 mol) at 20−25 °C to give the triazole aldehyde (139.0 g assay) in 90% assay yield (95% yield relative to sodium azide). No unreacted azide was detected by assay (LOD < 30 ppm).[21] 4-*N*,*N*-Dimethylaminomethyl-5-formyl-1,2,3-triazole was isolated from the same reaction mixture by any of the following three procedures.

Method A: Resin Column Isolation. The DMSO solution of triazole aldehyde (pH ≈ 9.7) was pH adjusted to 7.0 with aqueous HCl (1.0 N, ca. 2.0 L) and washed with ethyl acetate (1.0 L). The layers were separated, and the aqueous DMSO phase was loaded onto a column containing Dowex 50 W X8−100 (1.7 mequiv/mL wet, 5.5 equiv, 3.3 L) at a flow rate of 4 bed volumes per hour. The resin was then washed with 2 bed volumes of deionized water, and the product was eluted with a mixture of acetonitrile/water/triethylamine (6:3:1). After 1 bed volume (3.3 L) was eluted to the column displacing the water wash, the flow was stopped, and the column was equilibrated for 1 h. An additional 1.5 bed volumes (5.0 L) was eluted over an hour to provide a 97% recovery of the triazole aldehyde. The acetonitrile/water/triethylamine solution was concentrated under reduced pressure, and the solvent was switched to 2-butanol (until water < 0.5 vol %) to crystallize the product. The final volume was adjusted to 750 mL. The crystalline product was filtered, washed with 2-butanol (200 mL), and dried at 40 °C under vacuum with a nitrogen stream to afford pure 4-*N*,*N*-dimethylaminomethyl-5-formyl-1,2,3-triazole (125.0 g) in 81% overall yield from 1-(dimethylamino)-2-propyne and 85% overall yield from sodium azide.

Method B: Aliquat 336 Extraction Process. To the DMSO solution of triazole aldehyde (pH ≈ 9.7) was added Aliquat 336 (807.0 g, 2.0 mol) and toluene (2.0 L). The mixture was stirred for 0.5 h, and water was added (1.1 L). The layers were separated, and the aqueous phase was back-extracted twice with Aliquat 336 (200.0 g, 0.5 mol) in toluene (2.0 L). The combined organic layers were washed with water (820 mL) to remove excess DMSO. The resulting organic layer was washed with a 12.5 vol % of aqueous acetic acid solution (930.0 mL, 2.0 mol) to release the triazole aldehyde into the aqueous phase. The layers were separated, and the organic phase was washed once again with plain deionized water (365 mL). These combined extractions recovered the triazole aldehyde (124.0 g) in 89% overall assay yield from the crude DMSO solution. The aqueous solution was concentrated under reduced pressure, and the solvent was switched to 2-butanol (until water < 0.5 vol %) to crystallize the product. The final volume was adjusted to 750 mL. The crystalline product was filtered, washed with 2-butanol (200 mL), and dried at 40 °C under vacuum with a nitrogen stream to afford pure 4-*N*,*N*-dimethylaminomethyl-5-formyl-1,2,3-triazole (**3**) (102.5 g) in 67% overall yield based on 1-(dimethylamino)-2-propyne (70% relative to sodium azide).

Method C: Piperidine Dimer-Derivatization Process. The DMSO solution of triazole aldehyde (pH ≈ 9.7) was pH adjusted to 7.5−8.5 with the dropwise addition of anhydrous HCl in 2-propanol (4.2 N, ca. 460 mL, ca. 1.95 mol) over 15 min at room temperature. After completion of the addition, the resulting yellow slurry was concentrated to remove THF and 2-propanol. The mixture was filtered through a pad of Celite and rinsed with DMSO (285 mL). Piperidine (108.5 mL, 1.1 mol) in ethyl acetate (985 mL, 1 M solution) was added to the DMSO filtrate at room temperature over 2 h, and the mixture was aged for a further 16 h. The resulting slurry was filtered to afford product **25** as a white solid, which was washed with DMSO (300 mL) and ethyl acetate (500 mL), and dried at 40 °C under vacuum with a nitrogen stream to afford the dimer adduct **25** (171.5 g assay) in 75% yield based on 1-(dimethylamino)-2-propyne (79% relative to sodium azide). The piperidine adduct hydrolyzed on the analytical HPLC column and was assayed as triazole aldehyde equivalent: mp 182−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 2 H), 3.97 (d, J = 13.2 Hz, 2 H), 3.51 (d, J = 13.2 Hz, 2 H), 2.53−2.74 (m, 4 H), 2.35−2.47 (m, 4 H), 2.29 (s, 12 H); 1.32−1.59 (m, 12 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4; 129.6; 73.6; 54.0; 48.8; 45.4; 26.0; 23.9. Anal. Calcd for $C_{22}H_{40}N_{10}O$ (460.62) C, 57.37; H, 8.75; N, 30.41. Found: C, 59.32; H, 8.60; N, 31.50.

Piperidine adduct **25** (171.5 g assay, 0.373 mol) was slurried in 2-propanol/water (98/2, 1.1 L), and trifluoroacetic acid (57.4 mL, 0.745 mol) was added over 10 min at room temperature with cooling. The triazole aldehyde was liberated during the addition and crystallized as a white solid from the reaction mixture. The slurry was stirred for 2 h at room temperature. The solid was filtered, washed with 2-propanol (150 mL), and dried at 40 °C under vacuum with a nitrogen stream to afford pure 4-*N*,*N*-dimethylaminomethyl-5-formyl-1,2,3-triazole (**3**) (96.5 g) in 84% yield (63% overall isolated yield from 1-(dimethylamino)-2-propyne): mp 184−185 °C;^{1}H NMR (400 MHz, D_2O) δ 9.90 (s, 1 H), 4.42 (s, 2 H), 2.77 (s, 6 H);^{13}C NMR (100 MHz, D_2O) δ 188.3; 144.0; 137.6; 51.7; 42.6. Anal. Calcd for $C_6H_{10}N_4O$ (154.17) C, 46.74; H, 6.54; N, 36.34. Found: C, 46.50; H, 6.58; N, 36.61.

2-(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(*S*)-(4-fluorophenyl)morpholine (1). Sodium triacetoxyborohydride (95 wt %, 424.0 g, 1.9 mol) was added to anhydrous *N*,*N*-dimethylacetamide (DMAC) (650 mL), and the mixture was aged at room temperature for 0.5 h. The resulting cloudy solution was added in one portion to a cold (0−5 °C) solution of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine *p*-toluenesulfonic salt (**2**) (609.0 g, 1.0 mol) and 4-*N*,*N*-dimethylaminomethyl-5-formyl-1,2,3-triazole (**3**) (200.5 g, 1.3 mol) in DMAC (1.3 L). The mixture was warmed to room temperature, heated at 40 °C for 2 h, and cooled to room temperature. Aqueous hydrochloric acid (2.0 N, ca. 1.75 L, ca. 3.5 mol) was added to bring the pH down to 1.5−2.5. The mixture was heated again at 40 °C for 2 h, cooled to room temperature, and diluted with toluene (6.6 L). The aqueous layer was neutralized to pH ≈ 8.5−9.0 with aqueous sodium hydroxide (5.0 N, ca. 1.9 L). The layers were separated, and the organic phase was washed with water (2 × 3.0 L) and concentrated under reduced pressure to give **1** as a yellow oil (570.0 g assay) in 99% yield as the free base. The material was converted to the HCl salt without further purification. The crude oil was dissolved in toluene (2.2 L), and anhydrous hydrogen chloride (4.5 N in 2-propanol, ca. 215 mL, 0.97 mol) was added over 5 min at room temperature. *n*-Heptane (550 mL) was added in one portion. The mixture was seeded (0.5 wt %, 3.0 g) and aged for 2 h with stirring at room temperature. The remaining *n*-heptane (7.2 L) was added slowly over 2 h. The resulting slurry was aged for an additional 2 h at room temperature with stirring. The solid was filtered, washed with a 3:1 mixture of *n*-heptane/toluene (1.5 L), and dried at 40 °C under vacuum with a nitrogen stream to afford the pure **1** hydrochloride salt (575.5 g) in 95% yield as a white solid. $[\alpha]_D^{25}$ +163 (*c* 1.0, MeOH): mp 201−202 °C;^{1}H NMR (400 MHz, CD_3CN) δ 7.75 (s, 1 H), 7.54 (br t, J = 6.4 Hz, 2 H), 7.38 (s, 2 H), 7.11 (t, J = 8.8 Hz, 2 H), 4.90 (q, J = 6.6 Hz, 1 H), 4.34 (d, J = 2.8 Hz, 1 H), 4.21 (d, J = 14.1 Hz, 1 H), 4.15 (d, J = 14.1 Hz, 1 H), 4.10 (td, J = 11.4 and 2.4 Hz, 1 H), 3.69 (d, J = 13.9 Hz, 1 H), 3.56 (ddd, J = 11.4, 3.2, and 1.6 Hz, 1 H), 3.48 (br m, 1 H), 3.23 (d, J = 13.9 Hz, 1 H), 2.78 (s, 6 H), 2.74 (od, 1 H), 2.44 (br t, J = 12.0 Hz, 1 H), 1.44 (d, J = 6.4 Hz, 3 H);^{13}C NMR (100 MHz, CD_3CN) δ 163.5 (d, J = 244.0 Hz, Csp^2−F), 147.2, 142.3, 135.4, 134.1, 132.7 (d, J = 8.0 Hz), 131.9 (q, J = 32.9 Hz, Csp^2−CF_3), 127.9, 124.4 (q, J = 271.5 Hz, CF_3), 122.3, 116.0 (d, J = 21.7 Hz), 96.3, 73.1, 70.2, 60.1, 58.2, 53.0, 50.7, 49.4, 42.9, 24.5. Anal. Calcd for $C_{26}H_{29}ClF_7N_5O_2$ (611.98) C, 51.03; H, 4.78; N, 11.44. Found: C, 51.11; H, 4.67; N, 11.33.

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