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A VERSATILE SYNTHESIS OF A β-TURN PEPTIDOMIMETIC SCAFFOLD: AN APPROACH TOWARDS A DESIGNED MODEL ANTAGONIST OF THE TACHYKININ NK-2 RECEPTOR.

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Abstract: A general and stereocontrolled synthesis of an azabicyclo[4.3.0]nonane amino acid template with an appended substitutent at C-5 was developed. The approach allows for stereochemical and functional variations that extend the utility of these rigid amino acid motifs as peptidomimetics. The synthesis of a weakly active but specific NK-2 receptor antagonist is described. Copyright © 1996 Elsevier Science Ltd

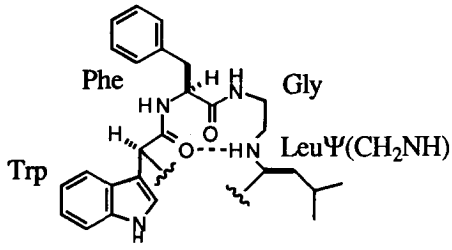
The tachykinins are a family of chemically related deca-, undeca-, and dodecapeptides that share a common C-terminal sequence (Phe-X-Gly-Leu-Met-NH_2, X= Phe, Tyr, Ile, or Val)[1] and possess a broad spectrum of similar biological properties.[2] There is general agreement that the multitude of biological effects induced by the tachykinins, such as pain and inflammation are mediated through three receptor subtypes designated NK-1, NK-2, and NK-3, for which substance P, neurokinin A, and neurokinin B are the respective endogenous ligands.[3] These observations have suggested that suitable tachykinin antagonists may be of significant therapeutic use in the treatment of clinical conditions ranging from arthritis, migraine, and asthma to postoperative pain and nausea. Extensive research has led to the discovery of several potent agonists and antagonists of the NK-1 and NK-3 type tachykinin receptors.[4] Selective antagonists to neurokinin A at the NK-2 receptor have also been reported, however, they are somewhat more elusive.[5] One such NK-2 antagonist reported recently was the homodetic cyclic peptide cyclo-[Gln-Trp-Phe-Gly-Leu-Met].[6] Solution-phase conformational analysis of a similar cyclic peptide cyclo-[Gln-Trp-Phe-Gly-LeuΨCH_2NH-Met][7] revealed the existence of a β-turn subunit involving the Trp-Phe-Gly-LeuΨCH_2NH residues **1**.[7] Based on these observations, we had previously designed and reported that the conformationally biased bicyclic lactam **2** exhibited high selectivity for tachykinin NK-2 receptor, although its activity was only modest (IC_{50}, 3μM).[8]

In view of this discovery, we wished to investigate the activity/selectivity relationship at the NK 1-3 receptor sites by positioning a variety of substituents around a similar rigid motif, as depicted in expression **3**. A further consideration we wished to address was the design of a peptidomimetic scaffold which could be utilized as a reference point for the generation of a β-turn peptidomimetic library *via* combinatorial chemistry.

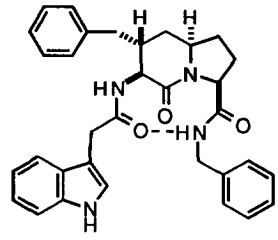
Three key requirements were established in order to achieve our desired goals: (a) The synthetic route must be versatile and flexible enough to permit the incorporation of a range of substituents both regio- and stereoselectively; (b) The formation of the bicyclic lactam should be mild, efficient and conducive to the positioning and stability of the pendant groups and (c) The peptidomimetic scaffold should contain suitable orthogonal protecting groups not

only for the acid and amine functionalities, but also for an additional substituent which could be linked to a polymer support.

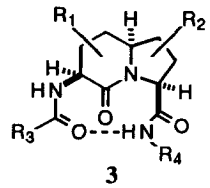
Figure 1



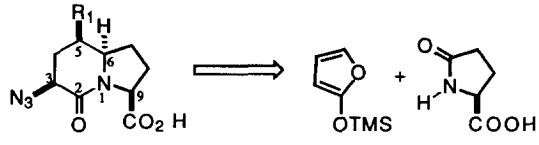
1, Type 1 β-turn (ref. 7)



2 (ref. 8)



3



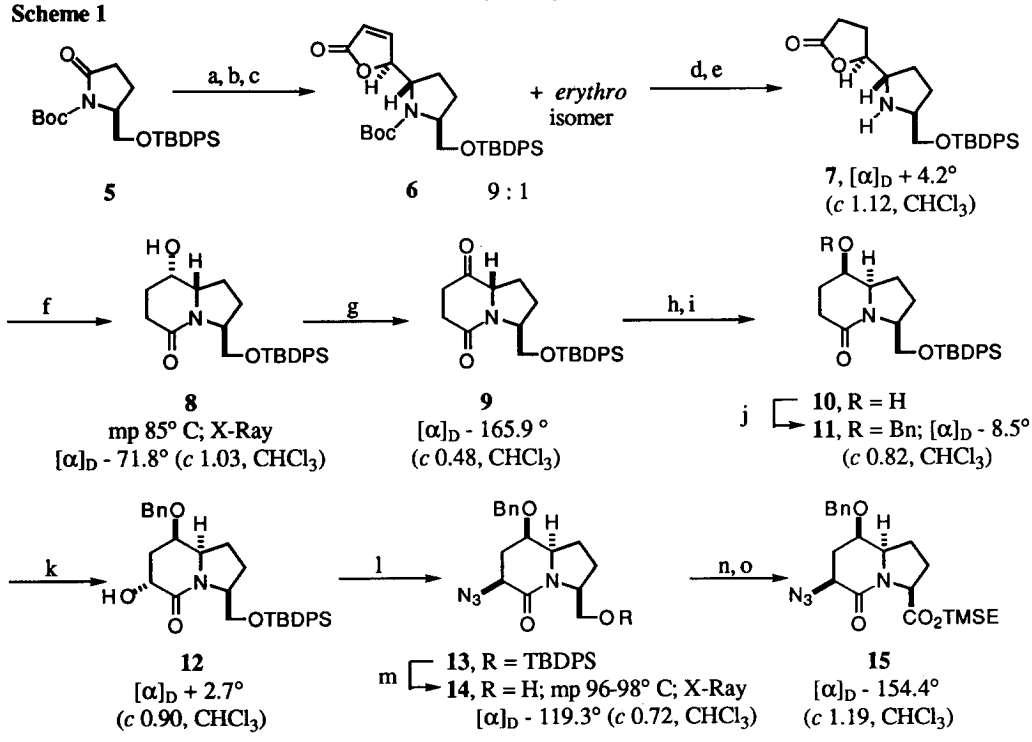
4, R_1= OBn

With these criteria in mind we proposed **4** as our desired target peptidomimetic nucleus. The use of this type of azabicyclo amino acid template as a mimic of β-turns has become increasingly fashionable.[9] Their synthesis in optically pure form has proven however to be challenging, most procedures resulting in a mixture of isomers. One notable exception, however, is the route recently described by Lubell and Lombart[10] to the N-Boc derivative of **4** without the C-5 substituent in high optical purity and in an expedient manner from glutamic acid. Our goals, however, required that the chosen route be highly flexible towards the topology of the template, the introduction of ring substituents as well as the presence of an appendage which could later be attached to a solid phase support. We report herein a general and stereocontrolled method for preparing the azabicyclo[4.3.0]nonane template by a condensation reaction between 2-(trimethylsilyloxy)-furan (TMSOF)[11] and a suitably functionalized precursor to an cyclic iminium ion[12] followed by a mild cyclization.

Pyrrolidinone **5** (Scheme 1), which was efficiently prepared from pyroglutamic acid,[13] was strategically used as our key chiron to gain easy access to substitituted core templates with high stereoselectivity (R_2 in **3**). Moreover model studies had revealed that the choice of protecting groups was crucial to both the facial selectivity and diastereoselectivity of the key Diels-Alder type condensation, the best combination being TBDPS with Boc. Reduction of **5** using either DIBAL-H or Superhydride® followed by methylation gave the protected hemiaminal as a 1:1 mixture of anomers in almost quantitative yield. The addition of a catalytic amount of $BF_3.Et_2O$ to the protected hemiaminal at low temperature in CH_2Cl_2 generated the required cyclic iminium ion which was trapped regioselectively in situ by TMSOF affording **6** and the *erythro* isomer in a 10:1 ratio (^1H NMR) in 91% yield from **5**.[14] The anticipated *threo* configuration for **6** was confirmed at a later stage in the synthesis. Hydrogenation of the mixture containing **6** to the saturated lactones, followed by removal of the Boc protecting group with bromocatechol borane[15] gave the lactone **7** and its diastereoisomer which were easily separated by chromatography and obtained in a ratio of approximately 10:1. Only the major diastereoisomer underwent cyclization upon heating in toluene, affording **8** in 89% yield.[16] The relative *threo* stereochemistry of compound **8** was assigned by NOE

studies which was further confirmed by single crystal X-ray analysis. It was found,

Scheme 1



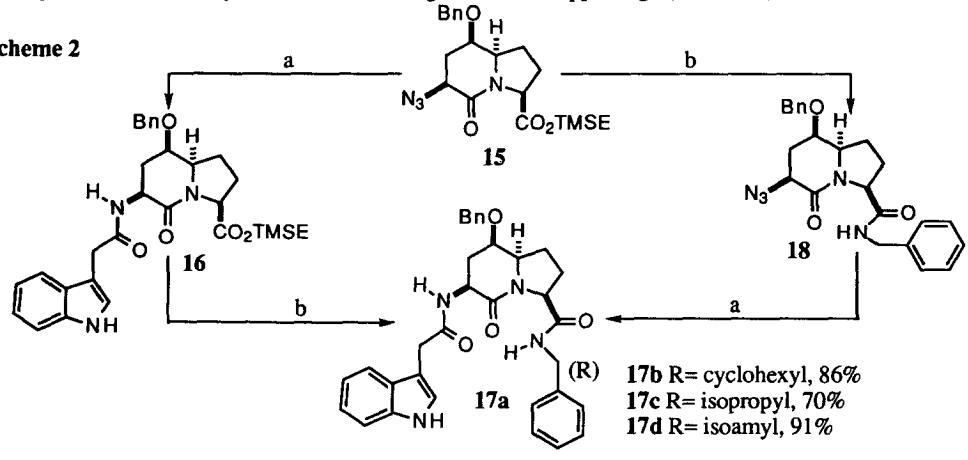
Reagents: (a) DIBAL-H (1.3 equiv), THF, -78 °C, 1 h; (b) MeOH, CSA (cat) 0 °C, 1h; (c) 2-(Trimethylsilyloxy)-furan (1.5 equiv), $BF_3.OEt_2$ (0.6 equiv), -78 °C, 1 h, 91% (3 steps); (d) H_2/1 Atm, Pd/C (5%), EtOAc, 2 h, 100%; (e) *B*-Bromocatechol borane (2 equiv), CH_2Cl_2, 0 °C; $NaHCO_3$, 84%; (f) MeONa (cat), MeOH, 0 °C, 1 h, 99%; (g) Dess-Martin periodinane (2 equiv), CH_2Cl_2, 1 h, 92%; (h) DBU (cat), benzene, ~70 °C, 30 min, 44% (91% based on recovered **11**); (i) $LiBEt_3H$ (1.3 equiv), THF, -78 °C to -50 °C, 3h; $NaHCO_3$, 30% H_2O_2, 92% (14:1); (j) NaH (1.4 equiv), THF, BnBr (5 equiv), TBAI (cat), 18 h, 100%; (k) ^tBuLi (1.6 equiv) 5 min, THF, -78 °C, $(MeO)_3P$ (2 equiv), O_2 flow, 20 min; NH_4Cl, 81%; (l) Ph_3P (5equiv), DEAD (5 equiv), 0° C, 5 min then $(PhO)_2P(O)N_3$ (5 equiv), 76%; (m) HF-py (cat), MeCN, 5 h, 91%; (n) Jones oxidation (10 equiv), acetone, 0 °C, 1 h, 86%; (o) EDCI (1.2 equiv), DMAP (1.2 equiv), 2-Trimethylsilyethanol (1.5 equiv), MeCN, 77%.

however, that both diastereoisomers could be converted into their respective bicyclic structures in almost quantitative yields using a catalytic amount of sodium methoxide in methanol at 0 °C. ^1H NMR studies indicated that the minor *erythro* diastereoisomer was epimeric at the hydroxyl center relative to **8**, implying that the reaction between TMSOF and the cyclic iminium ion had been completely face selective with respect to the iminium, as predicted by model studies. With this knowledge in hand, we perceived that we could obtain the desired azide functional group by first introducing a hydroxyl group in an electrophilic manner with high α-facial selectivity followed by a Mitsunobu type azidation reaction.[17] In order to invert the stereochemistry at the ring junction the alcohol group in **8** was initially oxidized in high yield to the ketone **9** using the Dess-Martin periodinane.[18] Although molecular modeling had predicted a 4 Kcal energy difference between the two possible ketone epimers in favor of the α-H isomer, the optimum epimerization conditions (DBU, benzene, Δ) gave only a 1:1 mixture of products. Fortunately, the two isomers were separable by chromatography and the starting ketone **9** could be

recycled. Reduction of **9** using sodium borohydride gave a 1:1 mixture of inseparable alcohols whereas Superhydride®, gave excellent α-facial selectivity (14:1) affording **10** in 92% yield. Benzylation gave **11** in quantitative yield and its relative stereochemistry was unambiguously assigned by detailed ^{1}H NMR studies. The introduction of the vital C-3 α-hydroxyl group utilizing the electrophilic Davis oxaziridine[19] reagent proved to be challenging. Initial hydroxylation studies on benzyl protected γ-valerolactam revealed that higher yields were obtained when lithium bases were used rather than the expected potassium bases (Li > Na > K). A 70% yield of hydroxylated lactam was obtained when LiHMDS was used followed by a rapid addition of a five fold excess of oxaziridine. Unfortunately, when these conditions were used on **11** only (12%) of compound **12** was isolated, with recovery of **11** (63%). When *tert*-butyllithium was used as the base, the hydroxylated product **12** was isolated in 79% yield. On scaling the reaction up, however, it was found necessary to add the enolate slowly to the Davis oxaziridine in order to obtain a reasonable yield of 60-65%. These hydroxylation problems were finally circumvented, however, when it was found that oxygen, in the presence of the enolate and trimethylphosphite, was an efficient source of the hydroxyl group.[20] Extensive ^{1}H NMR studies on **12** confirmed the anticipated orientation of the hydroxyl group and confirmed our hopes for a stereodirecting effect by the benzyloxy and TBDPS groups. Surprisingly **12** was found to be less polar than **11**, possibly due to hydrogen bonding between the hydroxyl group and the lactam carbonyl. Introduction of the azide group using diphenylphosphoryl azide[21] occurred with complete inversion (NOE studies), affording **13** in 76% yield. Removal of the TBDPS protecting group using the mild conditions of HF-pyridine in acetonitrile gave a crystalline solid **14** whose structure was unambiguously confirmed by single crystal X-ray analysis, thus confirming that all four stereocenters had now been correctly established. Jones oxidation of **14** gave the intended bicyclic β-turn peptidomimetic nucleus **4** in 86% yield. For the purposes of functional group diversification we prepared the 2-trimethysilylethyl ester **15** under standard EDCI conditions.

With **15** in hand we decided to prepare representative amide derivatives from the carboxy terminus, while maintaining an indole 3-acetyl motif as a resident group at the 3-position. Initially we decided to extend the left-hand appendage of **15** followed by attachment of the right-hand side appendage (Scheme 2).

Scheme 2



Reagents: (a) i. Pd/C, H_2/1 atm, NH_4OAc, 5 min, ii. Indole-3-acetic acid (1.5 equiv), BOP (1.5 equiv), MeCN, 0 °C, 1 h, 76%; (b) i. TBAF (1.5 equiv), THF, 0 °C, 1 h, ii. BOP (1.5 equiv), $BnNH_3Cl$, (1.5 equiv), MeCN, 0 °C, 1 h, 86%.

The azide was selectively reduced in the presence of the benzyl ether using standard hydrogenation conditions (Pd/C, H_2 1 atm, 5 min) but in the presence of a stoichiometric amount of NH_4OAc.[22] The resulting free amine was successfully coupled with indole-3-acetic acid under standard BOP conditions[23] to cleanly generate **16** in 76% yield over the 2 steps. Desilylation using TBAF gave the carboxylic acid (94%) that was readily transformed into the benzylamide **17** using BOP and benzylamine hydrochloride (92%). The overall yield for the preparation of **17** from the core structure **15** was 65% and no epimerization was detected in the products (NOE, noesy, and roesy studies). We also found that the order in which the appendages were chain-extended did not significantly alter the yield of the product (Scheme 2). With a reliable protocol in hand, we proceeded to prepare several model amide derivatives **17a-d** as shown in Scheme 2.

Receptor binding assays of compounds **17a-d** revealed selective antagonist activity for the benzylamide analog **17a** for the NK-2 receptor (49% at 1 μM).[24] In spite of the weak activity, it is of interest that no NK-1 or NK-3 binding was exhibited, hence the potential for further refinements of the prototype structure **17a**.

In summary, we have developed a stereocontrolled and versatile synthesis of a β-turn peptidomimetic nucleus. The oxygen substituent at C-5 adds to the versatility of such motifs, since it can modulate levels of hydrophilic binding, engage in H-bonding or be manipulated chemically. An obvious extension of this work involves the attachment of the bicyclic nucleus such as **15** to a solid support, and to entertain the introduction of a variety of groups at the carboxyl and amine appendages. These and related strategies for combinatorial chemistry are presently under investigation.

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