Synthesis of a Benzomacrolactone-Based Somatostatin Mimetic
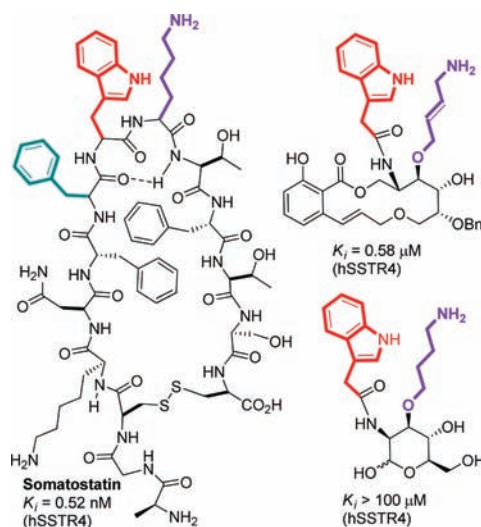
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ABSTRACT

The benzomacrolactone is a framework found in numerous natural products. The synthesis of an orthogonally functionalized benzomacrolactone from D-glucosamine and a salicylic acid derivative is described. This macrolactone was used for the synthesis of a somatostatin mimetic that has submicromolar affinity for the human somatostatin receptor 4 (hSSTR4).

A recent analysis of scaffolds investigated in organic chemistry has shown that a small number of frameworks are found in a large number of all known compounds.[1] This could, at least partially, explain why the diversity of scaffolds in a set of known drugs is considered to be low.[2] Hence the exploitation of frameworks less used to date in medicinal chemistry might ultimately lead to increased success in drug discovery. If the scaffolds are "natural product like", they could have increased biological importance.[3]

The low bioavailability and poor pharmacokinetics of somatostatin **1** has led to interest in nonpeptide mimetics which may be better drug candidates.[4] During the early 1990s, Hirschmann and colleagues at the University of Pennsylvania introduced the use of β-D-glucose, its enantiomers, and a diastereomer (β-D-mannose) as scaffolds for the synthesis of ligands for the somatostatin, the substance

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P, and the β_2-adrenergic receptors.[5] Since this contribution, monosaccharides,[6] due to their polyfunctional nature, have been a basis for generating a wide range of compounds for screening. The glucopyranoside **3** (Scheme 1) prepared by the Hirschmann group, and containing the lysine, tryptophan, and phenylalanine side chains of **1**, was found to be a ligand for somatostatin receptors, indicating that truncated mimetics are of interest. Other research has also indicated that interactions of the side chains of the Trp-Lys fragment of the hormone somatostatin **1** seem to be important for the recognition of SSTRs.[7]

Scheme 1
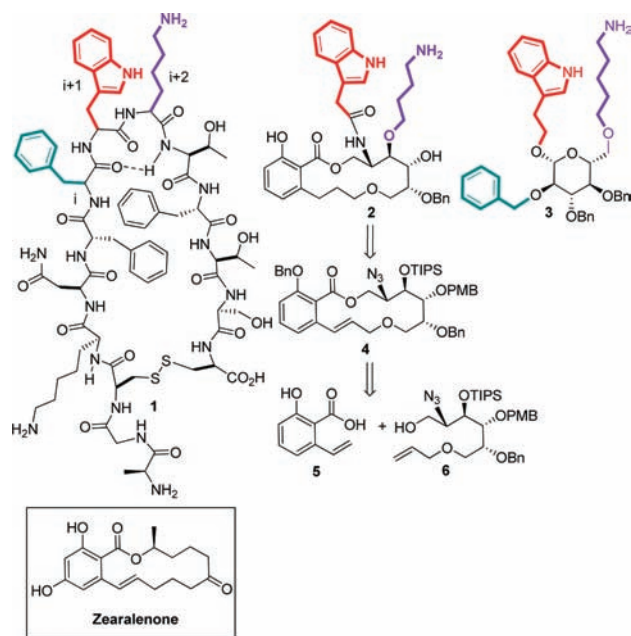
Herein we were interested in presenting groups on a benzomacrolactone scaffold that could mimic the interactions of the Trp-Lys fragment and selected **2** and analogues of **2** as targets for synthesis. There is no crystal structure available of somatostatin receptors binding to any ligands, but we hypothesized that the scaffold in **2** may span a larger surface of a protein receptor compared with a monosaccharide, which could lead to a ligand of higher affinity. Benzomacrolactones are common in nature (e.g., zearalenone,[8] Scheme 1), having a range of interesting biological properties,[9] and analogues would be of interest for screening. Herein we describe the synthesis of somatostatin mimetics from a suitably decorated benzomacrolactone **4**.

The preparation of **4** was envisaged (Scheme 1) from salicylic acid **5** and the alcohol **6**. The incorporation of azide, OTIPS, and OPMB (PMB = 4-methoxybenzyl) was based on providing the potential to introduce modifications selectively at these sites, with previous experience indicating orthogonality between the groups.[10]

Scheme 2
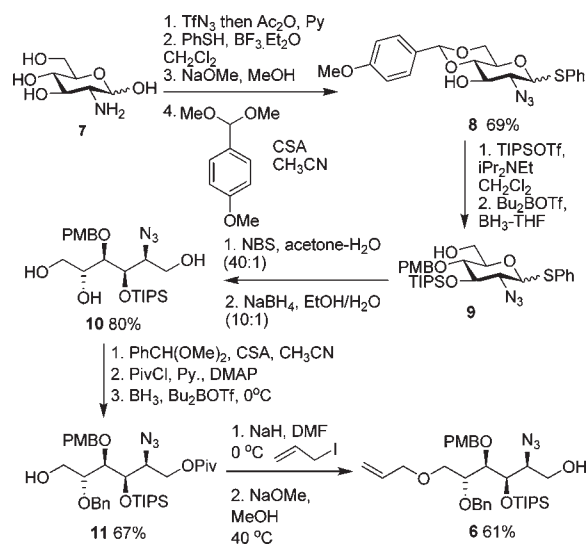
The synthesis of **6** (Scheme 2) commenced from D-glucosamine **7**. The fully acetylated 2-azido-2-deoxy-D-glucopyranose was obtained as a mixture of anomers (α:β, 2:1) after diazo transfer and subsequent per-O-acetylation.[11] A thioglycoside was then prepared,[12] and subsequent de-O-acetylation followed by reaction with dimethylanisaldehyde acetal and CSA gave **8**.[13] A TIPS protecting group was then introduced, and subsequent partial reductive cleavage gave **9**. Next, **9** was hydrolyzed.[14] If too high a proportion of water was used, it led to decomposition. The hemiacetal intermediate on reaction with $NaBH_4$ in $EtOH/H_2O$ then gave **10**.[15] The 1,2-diol of **10** was protected as a benzylidene acetal, and a pivalyl group was then introduced at the free alcohol group; subsequent partial reductive cleavage of the benzylidene acetal gave **11**. The allylation of the free alcohol was carried out using sodium hydride and allyl iodide. The pivalyl ester[16] was removed to give **6**.

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The preparation of the aromatic precursor **5** was next carried out (Scheme 3)[17,18] from commercially available **12**. Formation of the acetonide was first carried out, the resulting phenol was converted to its triflate, and a subsequent palladium-catalyzed coupling[19] with potassium vinyltrifluoroborate gave **13**. The acetonide **13** was then hydrolyzed to give **5**. Reaction of **5** with the sorbitol derivative **6** by a Mitsunobu esterification[20] promoted by triphenylphosphine in the presence of DIAD gave **14**. It is worth noting that the yield from the esterification decreased dramatically (from 83 to 45%) if the coupling was carried out starting from the benzyl ether **15**. The pK_a of **5** is lower than that of **15** due to intramolecular H-bonding in **5**, which explains the increased yield. The phenol was converted to its benzyl ether and then RCM[21] using the Hoveyda−Grubbs II catalyst in CH_2Cl_2 under argon gave **4** (85% from **14**). When **14** was directly subjected to RCM using the catalyst, the yield of the ring-closed product was low (∼40%). The optimum conditions for RCM were established after investigation of a variety of conditions,[22,23] and the Hoveyda−Grubbs II catalyst[24] was chosen. Separation of the catalyst from the product was difficult. Chromatography using toluene/CH_3CN (200:1) as a solvent led to separation of the catalyst and isolation of **4** (92%).

To obtain somatostatin mimetics, side chains containing an amino group and indole group were installed on the scaffold (Scheme 4). First, the azide of **4** was reduced using PMe_3,[25] which was more effective than PBu_3 or PPh_3. The resulting amine was then coupled with indol-3-ylacetic acid **16**[26] to give **17**. Next, the TIPS group was removed using TBAF in THF, and the resulting hydroxyl group alkylated using 1,4-dibromo-*trans*-2-butene **18** in the presence of Ag_2O[27] gave **19**. A variety of attempts to alkylate the secondary hydroxyl group using **20/21** failed. With the bromide **19** in hand, an amine surrogate then needed to be introduced. The Gabriel reagent (potassium phthalimide) was avoided as strongly basic conditions would have been possibly needed for removal of the phthalyl

group, and there was evidence of decomposition under such conditions. Various *N*-benzyl derivatives were prepared, but these approaches were ultimately unproductive, and finally, the use of potassium bis(*t*-butoxycarbonyl)amine (Boc$_2$NK) succeeded; its reaction with **19** giving **22** (77%).[28]

Scheme 4
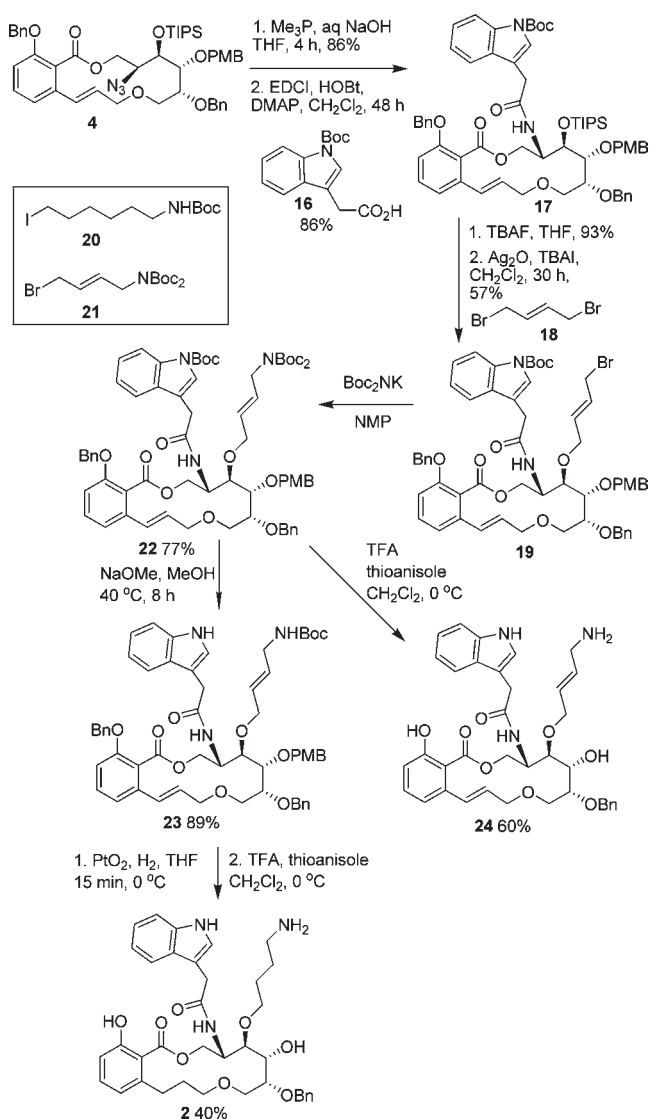
Scheme 3
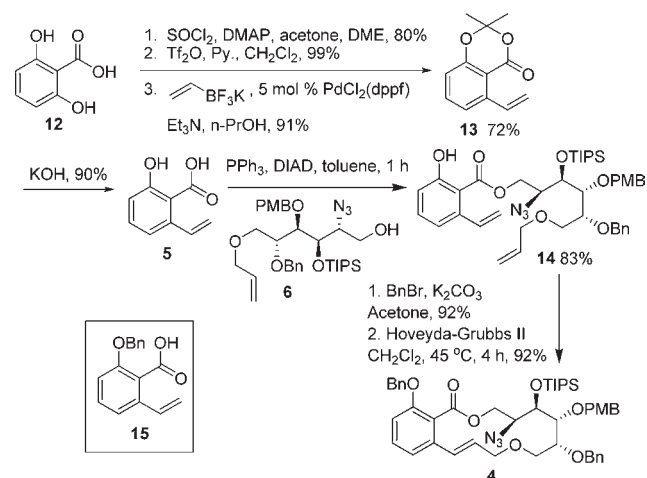
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Deprotection of **22** combined with reduction of the alkene groups was next investigated. In order to minimize the number of deprotection steps, trifluoroacetic acid (TFA) was first chosen as it could potentially remove the benzyl group from the phenol, as well as the Boc and PMB protecting groups in one pot.[29] The reaction of **22** with TFA in the presence of cation scavengers (PhSH, anisole, thioanisole) was screened,[30] and it was found that the use of thioanisole as a cosolvent with TFA led to the formation of **24** (60%), an analogue of **2**. The reduction of the alkene groups of **22** was next investigated. Hydrogenation (5 or 10% Pd−C with AcOH or HCl in MeOH; 5% $Pd(OH)_2$, AcOH−MeOH; Wilkinson's catalyst, EtOH, etc.) of **22** led to decomposition. Moreover, it was found for some reagents that reduction of the indole ring[31] of **22** (as evidenced by MS analysis) was a problem, possibly due to the presence of a Boc group on the indole nitrogen. Hence a variety of conditions were screened (H_2O, heat;[32] Cs_2CO_3, imidazole, CH_3CN;[33] MeONa, MeOH) in order to remove the Boc group. Finally, the indole Boc and a second Boc group from the aminobutylene were removed from **22** using Zémplen conditions[34] at 40 °C to provide **23**. Subsequent attempts at hydrogenation reactions with **23** were still problematic when Pd−C or $Pd(OH)_2$ was used. Fortunately, hydrogenation from **23** using PtO_2 gave the desired intermediate, and subsequent treatment with TFA and thioanisole gave the target mimetic **2**.

Somatostatin regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled receptors (SSTRs). A sample of **2** (< 95% purity) showed activity as a ligand for hSSTR4 ($K_i \sim 1\,\mu M$). Compound **24** (> 95% purity) was a ligand for hSSTR4 ($K_i = 0.58\,\mu M$) and hSSTR5 ($K_i = 1.1\,\mu M$). As the benchmark, **1** had K_i values of 0.52 nM (hSSTR4) and 0.75 nM (hSSTR5), whereas the mannosamine derivative **26**
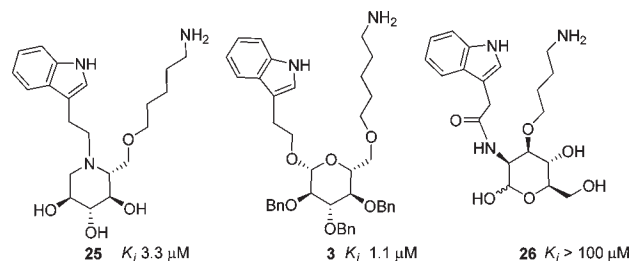

Figure 1. Somatostatin mimetics and affinities for hSSTR4.

(Figure 1, synthesis not shown) was inactive ($K_i > 100\,\mu M$) against these receptor subtypes. Previous work from the Hirschmann group showed that **3** is a ligand for hSSTR4 with a $K_i = 1.1\,\mu M$,[35] and work from our own group showed that **25** has a $K_i = 3.3\,\mu M$ against this receptor.[7b]

In summary, somatostatin mimetics based on benzomacrolactone scaffolds have been prepared. The approach could be extended to other peptidomimetics or other compounds for screening and broadens the potential for benzomacrolactone as a framework in bioorganic and medicinal chemistry.

Supporting Information Available. NMR spectra, selected experimental procedures and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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