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# Utilizing the intramolecular Fukuyama–Mitsunobu reaction for a flexible synthesis of novel heterocyclic scaffolds for peptidomimetic drug design

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Dedicated to the memory of Prof. Murray Goodman for a lifetime of scientific contributions and mentorship

**Abstract**—We report the synthesis of the novel scaffolds pyrazino[1,2-*b*]isoquinoline and pyrrolo[1,2-*a*]pyrazine displaying the somatostatin pharmacophores. Both classes of compounds contain a pyrazine heterocycle, which can be prepared in a straightforward manner utilizing an intramolecular Fukuyama–Mitsunobu reaction. As both the families derive from amino acids, they can be accessed in high optical purity.


As part of our efforts to design and synthesize compounds displaying an increased selectivity to the somatostatin subtype receptors and enhanced in vivo stability,[1–5] we were interested in a heterocyclic scaffold-based approach to somatostatin analogs.

Although the native peptide hormone itself shows strong binding in the nanomolar-range to the five receptors subtypes, it is essentially lacking any selectivity for the respective subtypes.[6] Much progress has been made in the design of small molecules that bind effectively and selectively to one of the five known subtypes of the somatostatin receptor families.[7] Some of the small molecule somatostatin analogs reported in the literature (Fig. 1) have been shown to bind in vitro to a specific receptor subtype with selectivities of up to five orders of magnitude over the other four receptors.[8,9] It could be argued that the molecular topology of these compounds has little in common with the structural features of the Phe[7]-Trp[8]-Lys[9]-Thr[10] unit of somatostatin which has been shown to be the pharmacophore region of the peptide hormone.[10,11]

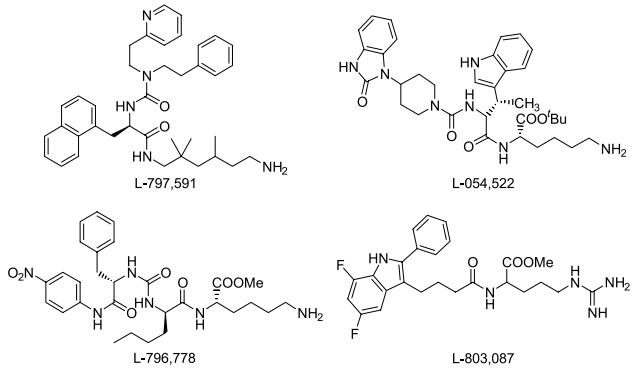


**Figure 1.** Compounds which have been shown to selectively bind with high affinity to one of the five human somatostatin receptor subtypes.

Inspired by the promising results of these small molecule somatostatin analogs, we intended to extend this work by a scaffold-based approach to nonpeptide somatostatin analogs. Recently, we were successful in designing and preparing scaffold-based compounds which selectively bound to the μ- and δ-opioid receptors.[12] We were mindful to design a scaffold that could incorporate a variety of functionalities in an appropriate three-dimensional arrangement and would allow late-stage diversification. These concepts are of paramount interest to facilitate the study of structure–activity relationships to optimize the potency and selectivity of target molecules.

*Keywords*: Scaffolds; Pyrazino[1,2-*b*]isoquinoline; Pyrrolo[1,2-*a*]pyrazine; Fukuyama–Mitsunobu; Peptidomimetics.
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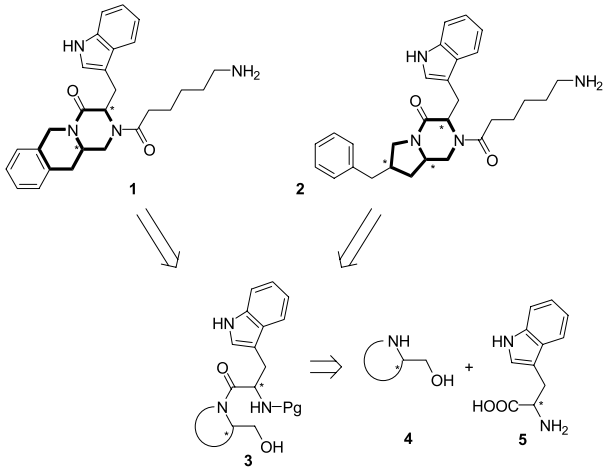
Our design focused on two structurally related scaffolds, the pyrazino[1,2-*b*]isoquinoline **1** and the pyrrolo[1,2-*a*]pyrazine **2** scaffold decorated with the pharmacophores of somatostatin analogs that relate to the native peptide: the indole nucleus, the aminoalkyl chain, and the commonly occurring aromatic moiety (Scheme 1). The attachment of the aminoalkyl chain to the secondary amine was to occur among the last synthetic steps. This strategy provided an advanced intermediate which could be utilized for structure–activity studies of the alkyl chain. Ring closure to produce the piperazine core was to be accomplished via alcohol through a Mitsunobu-related reaction. Alcohol **3** was to derive from an amide-bond formation utilizing the corresponding amino alcohol **4** and tryptophan **5**.

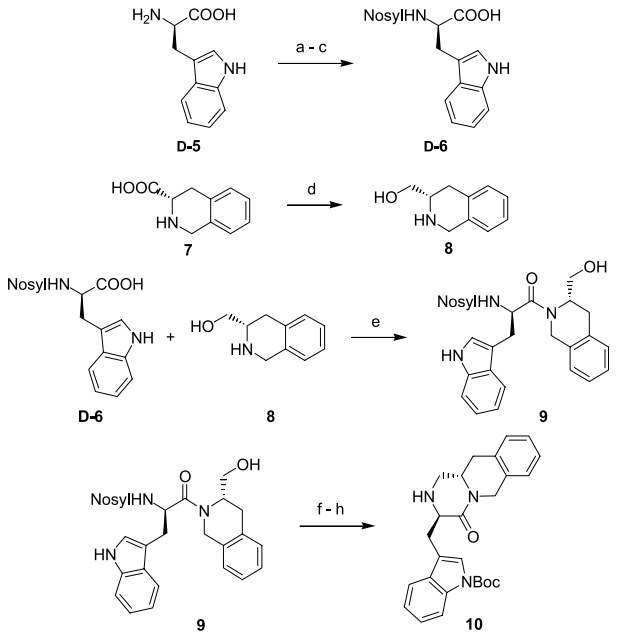
The key step in this reaction scheme is the cyclization reaction furnishing the protected cyclic secondary amine on the piperazine ring. It was our intention to take advantage of a protecting group which allowed us to form this carbon–nitrogen bond. Derivatization of amines as the corresponding 2-nitro-benzenesulfonamide (nosyl-amide) allows the formation of C–N bonds under Mitsunobu conditions utilizing alcohols.[13] Previously, related scaffolds were synthesized by a similar route albeit for application toward solid-phase chemistry.[14–16]

Synthesis of target compound **1** commenced with D-tryptophan **5** (Scheme 2) which was converted into its methyl ester and subsequently allowed to react with 2-nitro-benzenesulfonyl chloride in the presence of triethylamine yielding the protected tryptophan. Saponification of the methyl ester provided acid **D-6** in 80% yield over the three steps.

Amine **8** was obtained from the corresponding enantiomerically pure (*S*)-tetrahydroisoquinoline carboxylic acid (TIC, **7**) which was reduced utilizing borane methylsulfide complex in the presence of boron trifluoride diethyl etherate in THF.[17] After recrystallization, the amino alcohol **8** was obtained in 78% yield. The optical rotation was in agreement with the value reported in literature.[18]




**Scheme 1.** Retrosynthetic analysis of target structures **1** and **2**.




**Scheme 2.** Reagents: (a) $SOCl_2$, MeOH; (b) 2-nitro-benzenesulfonyl chloride, $Et_3N$, DCM, 80%; (c) LiOH, MeOH, $H_2O$, quant.; (d) $BF_3{\cdot}OEt_2$, $BH_3{\cdot}SMe_2$, THF, 78%; (e) EDC, HOBt, $Et_3N$, DMF, 77%; (f) DIAD, $PPh_3$, THF; (g) $Boc_2O$, DMAP, $CH_3CN$; and (h) PhSH, DBU, DMF, 41%, three steps.

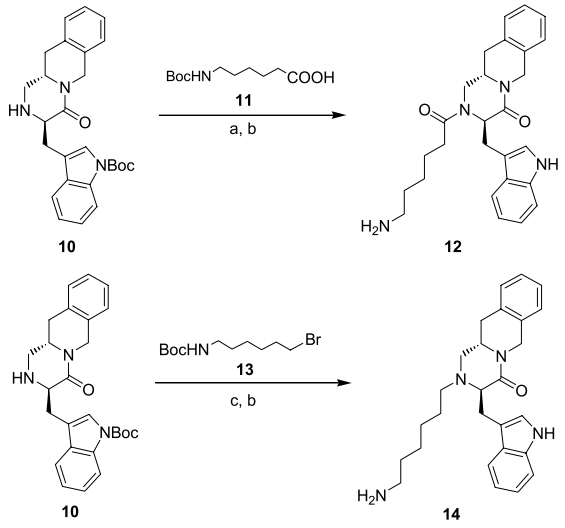
Amide **9** was formed in good yield (77%) from acid **D-6** and amine **8** utilizing 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) as the coupling reagents in DMF. As determined by $^1H$ NMR, a single diastereomer was produced for amide **9** which confirms the enantiopurity of amino alcohol **8**.

Amide **9** set the stage for the intramolecular Fukuyama–Mitsunobu reaction to form the protected piperazinone structure. Diisopropyl azodicarboxylate (DIAD) together with triphenylphosphine was utilized to accomplish the cyclization reaction. Following the intramolecular cyclization reaction, the indole ring was Boc-protected[19] yielding the indolylmethyl substituted tricyclic structure.

Among the various methods for the removal the nosyl group reported in the literature, the use of thiophenol in the presence of DBU was found to be the method of choice for our purposes. This reagent combination allowed the removal of the nosyl-protecting group producing the cyclic secondary amine **10** in a 41% yield over the three steps.

Amine **10** was acylated utilizing the amine-protected acid **11** to produce the fully protected target structure (Scheme 3). To minimize the steric bulk of the activated carboxylic acid, PyBroP was employed as the coupling reagent providing the desired amide in 80% yield. Subsequently, the protecting groups were removed from the fully protected structure with 4 N HCl in dioxane producing target compound **12**.

Alkyl bromide **13**, prepared from acid **11**,[20] was utilized to alkylate the secondary amine **10** in the presence of



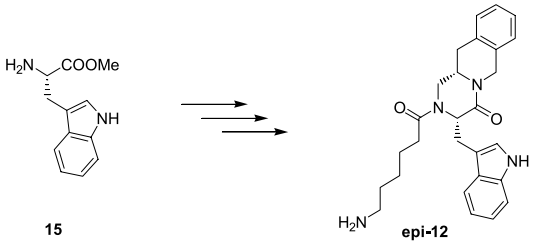

**Scheme 3.** Reagents: (a) **11**, PyBroP,$Et_3N$, DMF, 80%; (b) 4 N HCl, dioxane, quant.; and (c) **13**, DIEA, DMF, 31%.

diisopropylethyl amine at elevated temperature producing the tertiary amine. The removal of the protecting groups from this compound was accomplished quantitatively with 4 N HCl in dioxane producing target compound **14**.

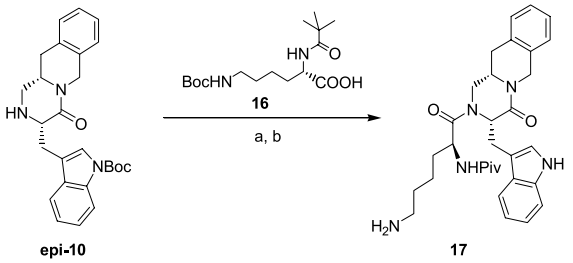
Utilizing the same synthetic procedure leading to compound **14** the corresponding diastereomer **epi-12** (Scheme 4) was obtained starting from commercially available L-tryptophan methyl ester **15**.

Intermediate **epi-10**, which is diastereomeric to secondary amine **10**, lends itself for introduction of an element of diversity as well. Coupling of lysine derivative **16**, which is acylated as a pivaloyl amide at the α-amine and Boc-protected at the ε-amine, gave rise to the corresponding amide in a moderate yield. Incorporating the sterically demanding pivaloyl amide side chain should reduce the overall flexibility of the final target structure **17**, which was obtained after deprotection with 4 N HCl in dioxane (Scheme 5).

As indicated above, we contemplated a second class of scaffolds which could serve as the basis for novel non-peptidic somatostatin analogs. This scaffold is based on a 1,4-diaza-2-keto-bicyclo[4.3.0]-nonane moiety **2** containing three asymmetric centers. As indicated in Scheme 1, substituted prolinol **4** and tryptophan **5** serve as starting materials from which the scaffold was to be




**Scheme 4.** The synthesis of **epi-12** was carried out using L-tryptophan.

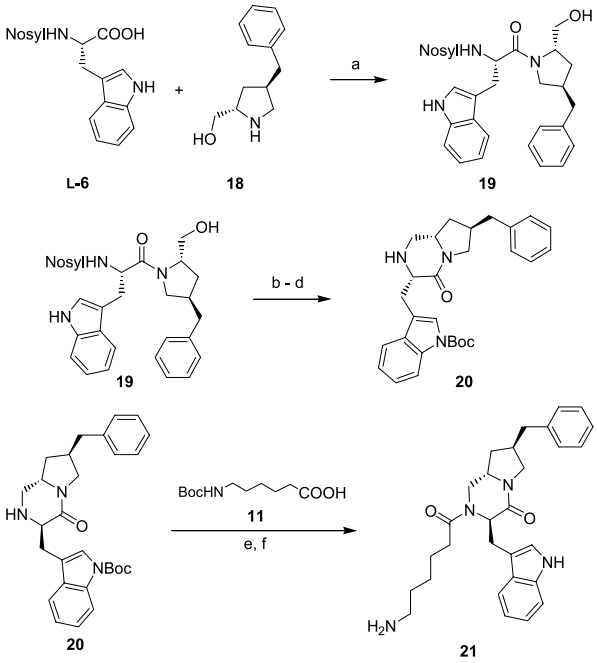



**Scheme 5.** Reagents: (a) **16**, PyBroP, $Et_3N$, DMF, 27%; (b) 4 N HCl, dioxane, quant.

synthesized. We recently reported on the asymmetric synthesis of protected 4-alkylprolinols and prolines.[21,22] Our newly developed method allowed for the effective and diastereoselective incorporation of a wide range of substituents onto the pyrrolidine ring.

With enantiomerically pure (2*S*,4*R*)-4-benzylprolinol **18** available, the amine was coupled to previously synthesized nosyl-protected tryptophan **L-6** utilizing EDC and HOBt as the coupling reagents in the presence of triethylamine (Scheme 6). Amide **19** was obtained in 62% yield and as a single diastereomer as determined by $^1H$ NMR.

Subsequently, the amide **19** was cyclized under Fukuyama–Mitsunobu conditions furnishing the bicyclic core. Boc-protection of the indole ring followed by removal of the nosyl-protecting group produced the secondary amine **20**.




**Scheme 6.** Reagents: (a) EDC, HOBt, $Et_3N$, DMF, 62%; (b) DIAD, $PPh_3$, THF; (c) $Boc_2O$, DMAP, $CH_3CN$; (d) PhSH, DBU, DMF, 33%, three steps; (e) **11**, PyBroP, $Et_3N$, DMF, 80%; and (f) 4 N HCl, dioxane, quant.

As before, the aminoalkyl side chain was installed via an amide bond utilizing protected aminohexanoic acid **11**. The amide-bond formation was carried out with PyBroP as the coupling reagent thus providing the fully protected target structure in 80% yield. The final molecule **21** was obtained in quantitative yield by treating this amide with 4 N HCl in dioxane.

Figure 2 summarizes the five target structures synthesized. On the basis of their elements of diversity, we hope to be able to answer relevant questions with regard to the utility of our designed scaffold. The main issues which can be addressed with this series of somatostatin analogs revolve around regiochemistry, stereochemistry, steric constraints, and charge.

Valuable information about the stereochemical requirements for the tryptophan moiety will be obtained by comparing somatostatin analog **12** with **epi-12**. Compound **14** contains a tertiary amine which will be protonated under physiological conditions. This structural feature will enable us to draw conclusions about the effects of a positive charge in the somatostatin ligand. Analog **17**, with the additional pivaloyl amide feature, follows the established trend of incorporating steric hindrance to the ligand therefore reducing the overall flexibility of the compound and thus increasing its binding affinity. Bicyclic structure **21** with the substituted prolinol building block represents a member of a potentially large family of somatostatin analogs based on the 1,4-diaza-2-keto-bicyclo[4.3.0]-nonane scaffold.

The design and successful synthesis of these two novel scaffolds are not limited to the area of somatostatin. As was shown previously, we have full control over the stereochemical properties of these scaffolds as well as the substituents which serve as pharmacophores. We believe that the facile and efficient syntheses of these scaffolds will lend themselves to the design of related nonpeptidic analogs of other biologically relevant structures.

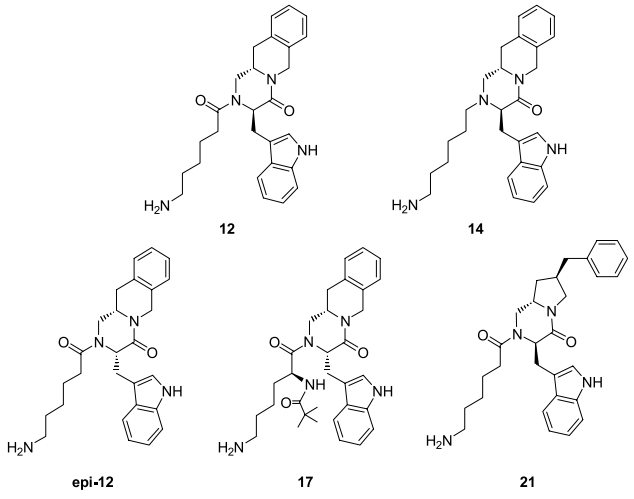



**Figure 2.** Series of compounds prepared by means of the intramolecular Fukuyama–Mitsunobu reaction.

## References and notes


1. Falb, E.; Salitra, Y.; Yechezkel, T.; Bracha, M.; Litman, P.; Olender, R.; Rosenfeld, R.; Senderowitz, H.; Jiang, S.; Goodman, M. *Bioorg. Med. Chem.* **2001**, *9*, 3255.
2. Mattern, R. H.; Moore, S. B.; Tran, T. A.; Rueter, J. K.; Goodman, M. *Tetrahedron* **2000**, *56*, 9819.
3. Mattern, R.-H.; Tran, T.-A.; Goodman, M. *J. Med. Chem.* **1998**, *41*, 2686.
4. Tran, T.-A.; Mattern, R.-H.; Afargan, M.; Amitay, O.; Ziv, O.; Morgan, B. A.; Taylor, J. E.; Hoyer, D.; Goodman, M. *J. Med. Chem.* **1998**, *41*, 2679.
5. Melacini, G.; Zhu, Q.; Osapay, G.; Goodman, M. *J. Med. Chem.* **1997**, *40*, 2252.
6. Janecka, A.; Zubrzycka, M.; Janecki, T. *J. Pept. Res.* **2001**, *58*, 91.
7. Rohrer, S. P.; Birzin, E. T.; Mosley, R. T.; Berk, S. C.; Hutchins, S. M.; Shen, D.-M.; Xiong, Y.; Hayes, E. C.; Parmar, R. M.; Foor, F.; Mitra, S. W.; Degrado, S. J.; Shu, M.; Klopp, J. M.; Cai, S.-J.; Blake, A.; Chan, W. W. S.; Pasternak, A.; Yang, L.; Patchett, A. A.; Smith, R. G.; Chapman, K. T.; Schaeffer, J. M. *Science* **1998**, *282*, 737.
8. Yang, L.; Guo, L.; Pasternak, A.; Mosley, R. T.; Rohrer, S. P.; Birzin, E. T.; Foor, F.; Cheng, K.; Schaeffer, J. M.; Patchett, A. A. *J. Med. Chem.* **1998**, *41*, 2175.
9. Yang, L.; Berk, S. C.; Rohrer, S. P.; Mosley, R. T.; Guo, L.; Underwood, D. J.; Arison, B. H.; Birzin, E. T.; Hayes, E. C.; Mitra, S. W.; Parmar, R. M.; Cheng, K.; Wu, T.-J.; Butler, B. S.; Foor, F.; Pasternak, A.; Pan, Y.; Silva, M.; Freidinger, R. M.; Smith, R. G.; Chapman, K. T.; Schaeffer, J. M.; Patchett, A. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 10836.
10. Vale, W.; Brazeau, P.; Rivier, C.; Brown, M.; Boss, B.; Rivier, J.; Burgus, R.; Ling, N.; Guillemin, R. *Recent Progr. Horm. Res.* **1975**, *31*, 365.
11. Nutt, R. F.; Veber, D. F.; Curley, P.; Saperstein, R.; Hirschmann, R. *Int. J. Pept. Protein Res.* **1983**, *21*, 66.
12. Creighton, C. J.; Zapf, C. W.; Bu, J. H.; Goodman, M. *Org. Lett.* **1999**, 1407.
13. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
14. Swayze, E. E. *Tetrahedron Lett.* **1997**, *38*, 8643.
15. Kung, P. P.; Swayze, E. *Tetrahedron Lett.* **1999**, *40*, 5651.
16. Arya, P.; Wei, C. Q.; Barnes, M. L.; Daroszewska, M. *J. Comb. Chem.* **2004**, *6*, 65.
17. Aggarwal, V. K.; Humphries, P. S.; Fenwick, A. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2883.
18. Yamaguchi, R.; Hamasaki, T.; Sasaki, T.; Ohta, T.; Utimoto, K.; Kozima, S.; Takaya, H. *J. Org. Chem.* **1993**, *58*, 1136.
19. Nakamura, K.; Baker, T. J.; Goodman, M. *Org. Lett.* **2000**, *2*, 2967.
20. Bromide **13** was prepared from acid **11** via reduction of acid **11** using borane methyl sulfide complex (78%) followed by bromination utilizing triphenylphosphine, bromine, and imidazole (78%).
21. Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2003**, *68*, 3923.
22. Del Valle, J. R.; Goodman, M. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1600.