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Synthesis of 2,4,5-Trisubstituted Tetrahydropyrans as Peptidomimetic Scaffolds for Melanocortin Receptor Ligands

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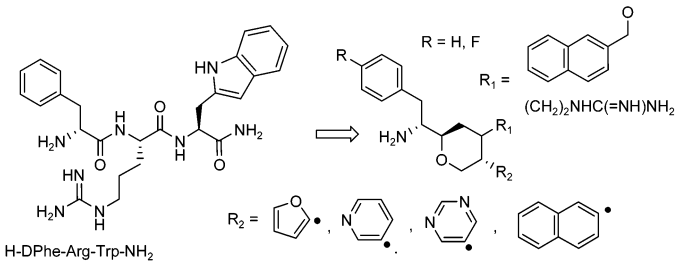
ABSTRACT



We have synthesized a series of 2,4,5-trisubstituted tetrahydropyran derivatives to determine the utility of this scaffold as a peptidomimetic platform. The key synthetic steps involved a palladium-mediated cross-coupling reaction of a dihydropyran-4-one moiety to introduce R_2 followed by a sequential regio- and diastereoselective reduction of sp^2 carbon centers. Selected compounds have shown biological activity at melanocortin receptors, indicating that this scaffold may be useful in the design of peptidomimetics relating to a tripeptide structure.

Creation of structures that can be used as peptide surrogates in drug discovery is a vibrant area of organic chemistry. Of particular interest are the constrained scaffolds that allow for a wide-ranging display of substituents in both regio- and stereochemical fashion. Analogues having a specific spatial distribution of substituents are useful in defining a preferred conformational state of receptor ligands for activity. The ready opportunity for a choice of substitutions and stereochemical characteristics of the substituted tetrahydropyran moiety makes this scaffold an interesting target in petidomimetic research. Herein we present one class of such compounds comprising 2,4,5-trisubstituted tetrahydropyran derivatives. Figure 1 shows that **3** can be viewed as a transformation of an amide bond **1** in which nitrogen and oxygen atom sites are constrained in a six-membered ring. In this sense, the construct **3** is also related to the known amide bond hydroxyethylene isostere **2**.[1]

We were therefore interested in the study of structure **3** to understand if it actually would show some biological properties of a tripeptide molecule. To verify this concept, we selected, in conjunction with our ongoing research in the melanocortin receptor area,[2,3] a benchmark tripeptide, H-

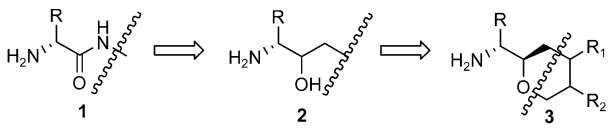


Figure 1. Correlation between amide bond **1**, amide bond isostere **2**, and the tetrahydropyran moiety **3**.

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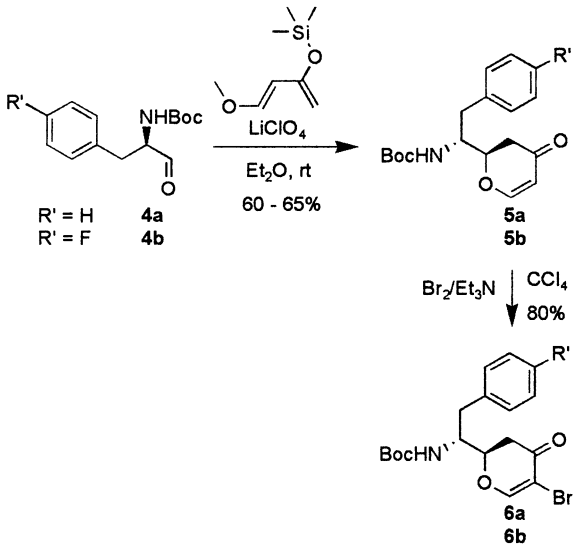
DPhe-Arg-Trp-NH_2. This peptide is a truncated version of the agonist message sequence His-Phe-Arg-Trp at the melanocortin receptor-4 (MC4R)[4] that was proposed as a target for the treatment of obesity[5,6] and sexual dysfunction.[7] For designing the synthetic targets, we chose 2-naphthylalanine, a bioisosteric replacement of tryptophane, because, for synthetic reasons, we preferred to introduce the naphthyl moiety rather than an indole into the anticipated mimetics. Inspection of H-DPhe-Arg-Trp-NH_2 reveals that if R is considered to be the benzyl group in **3**, then R_1 and R_2 should correspond to the side-chains of naphthylalanine and arginine. The melanocortin literature also indicated that the guanidine group might not be essential in MC4R nonpeptide agonists if a heterocyclic substituent is present in a proper position.[8] Furthermore, a halo atom in the phenylalanine moiety has been reported to modify agonist potency or produce an antagonist at MCR.[9] We incorporated these elements into our synthetic plan.

It should be noted that our definition of peptidomimetics is more functional than structural even though the design of 2,4,5-trisubstituted pyran analogues was based on the model peptide structure. While one may find certain structural similarities between the peptide and the structures presented later in this paper, we cannot prove that these compounds relate to any conformations of the peptide. In fact, there is no general definition of peptidomimetics, as their structures encompass a broad range of variations[10] and ligands can bind to different conformational ensembles of the target receptor.[11,12]

The first part of our synthesis, shown in Scheme 1, involved a formation of the 5-bromo dihydropyran-4-one derivatives **6a** and **6b**, providing 4- and 5-positions activated for further derivatization. En route to these products, we obtained dihydropyran-4-ones **5a** and **5b** using a known hetero Diels−Alder reaction of aldehydes[13] **4a** and **4b**, respectively. The latter materials were derived from D-phenylalanine, which represents the N-terminus of the model tripeptide. The major isomer of each dihydropyran-4-one was produced in a 5:1 excess over its diastereoisomer, in agreement with published data.[13]

Scheme 1



A halide at C5 was important as an activator for a palladium-mediated cross-coupling reaction[14] that we envisioned for introduction of aromatic substituents in this position. In a similar system, cis-2,3-disubstituted dihydropyran-4-one,[15] 5-iodo derivatives were used in this reaction. On the other hand, both bromo and iodo derivatives were used in cross-coupling reactions involving benzopyranones.[16,17] We were not able to obtain stable 5-iodo derivatives from **4a** and **4b**, and we turned our attention to 5-bromo dihydropyranes **6a** and **6b**. A traditional method of enone bromination using Br_2/Et_3N[18] proved to be very effective, with **5a** and **5b** giving the corresponding bromides in good yields. In contrast, attempts to make **6a** and **6b** with $PhI(OAc)_2$/TMSBr as reported for cis-2,3-disubstituted dihydropyran-4-one[15] led to a mixture of unidentified byproducts.

With 5-bromo dihydropyran-4-ones **6a** and **6b** in hand, we explored two variants of cross-coupling methodology to introduce R_1. First, we tried to utilize the trimethylstannane derivative[15] of pyranone **7**, since a large number of heteroaryl halides (Het-X) were readily available for further cross-coupling reactions. Unfortunately, low yields of **7** discouraged us from further explorations of this route and we employed the 5-bromo dihyropyran-4-one **5a** and heteroaryl stannanes as the cross-coupling components to make **8a**−**c**. The 2-naphthyl derivative **9**, on the other hand, was obtained by a Suzuki-type reaction involving 2-naphthyl boronic acid. The results of these reactions are reported in Table 1.

The next crucial aspect of our investigation was to determine if reduction of the double bond and the ketone

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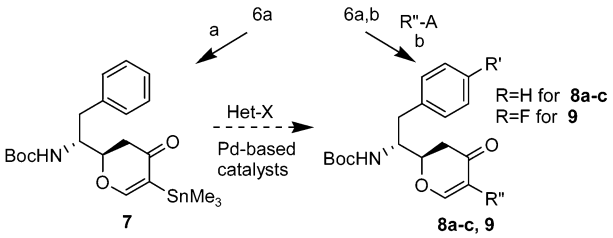
Table 1. Transformations of 5-Bromo Dihydropyran-4-one **6a** and **6b** and Related Compounds

R'	R''	A	product % yield	product % yield %de[a]	product % yield %de[a]
H **6a**		$SnMe_3$	**8a** 80	**10a** 80 >95	**11a** 90 87
H **6a**		$SnMe_3$	**8b** 55	**10b** nd nd	**11b** 65[b] 73
H **6a**		$SnMe_3$	**8c** 63	**10c** 60 75	**11c** 80 >95
F **6b**		$B(OH)_2$	**9** 61	**10d** 83 71	**11d** 90 >95

[a] De values were determined by NMR and HPLC. [b] Yield for two steps.

group could be performed in a sequential chemoselective and diastereoselective manner. We were particularly interested in reducing the double bond first because it would allow for keeping an active carbonyl for further modifications. The chemoselective reductions of this bond in pyrane-4-ones have been reported by means of hydrogenation[19−25] and L-selectride for the unsubstituted 5-position.[26] We chose L-selectride with the hope that it could provide chemoselectivity for double-bond reduction in the first case and diastereoselectivity in both cases (Scheme 3).

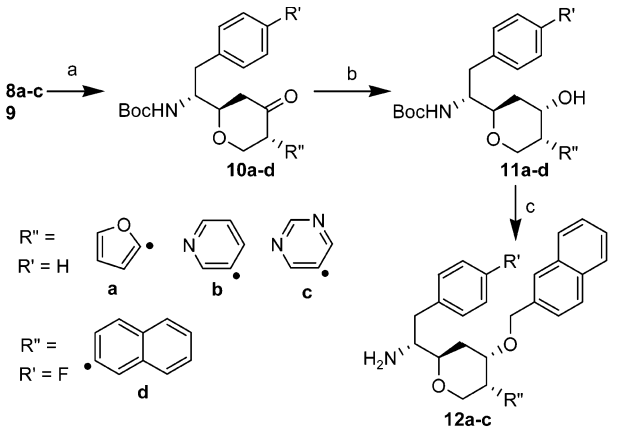
Scheme 2[a]



[a] Reagents and conditions. (a) $(Me_3Sn)_2$, PhMe, $Pd(Ph_3P)_4$, 85 °C, 3 h (10%). (b) **8a**−**c**: R′′−A, $Pd(PPh_3)_4$, DMF, 100 °C, 6 h. **9**: R′′−A, Na_2CO_3, $Pd(PPh_3)_4$, benzene, reflux 3 h. See Table 1 for yields.

Indeed, as shown in Table 1, the reactions are both chemo- and diastereoselective. The stereochemistry assignment of

Scheme 3[a]



[a] Reagents and conditions. **10a**−**d**: L-Selectride, THF, −78 °C. **11a**−**d**: L-Selectride, THF, −78 °C. **12a**−**c**: (i) 2-bromomethylenenaphthalene, NaH, Bu_4NI, THF; (ii) TFA, DCM.

products **11a**−**d** was based on the X-ray structure of **11a** (Figure 2) and their nuclear magnetic resonance spectra.

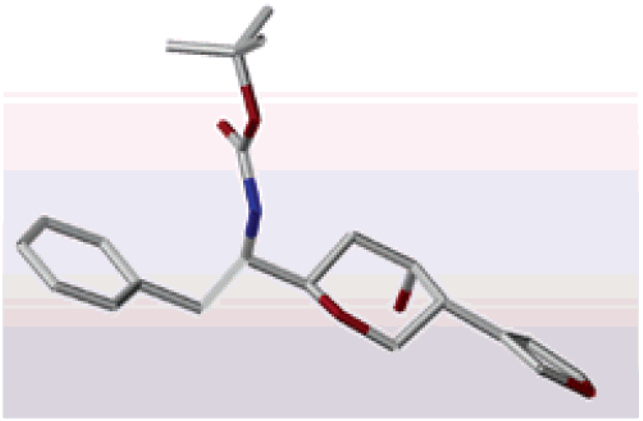


Figure 2. Model of **11a** generated from its X-ray structure.

Alkylation of **11a**−**c** to the corresponding **12a**−**c** concluded the synthesis of this series of potential tripeptide mimetics.

Scheme 4 shows the synthesis of structures in which the guanidylethyl moiety at C4 and 2-naphthyl at C4 correspond to the arginine and naphthylalanine sites in H-DPhe-Arg-(2-Nal)-$NHCH_3$.

The guanidyl substituent was introduced in a sequence involving a Horner−Emmons reaction[27] and a reduction of the resulting olefin as the key steps. The latter reaction was performed using a palladium catalyst formed in situ by reducing $PdCl_2$ with $NaBH_4$[28] and produced two diastereo-

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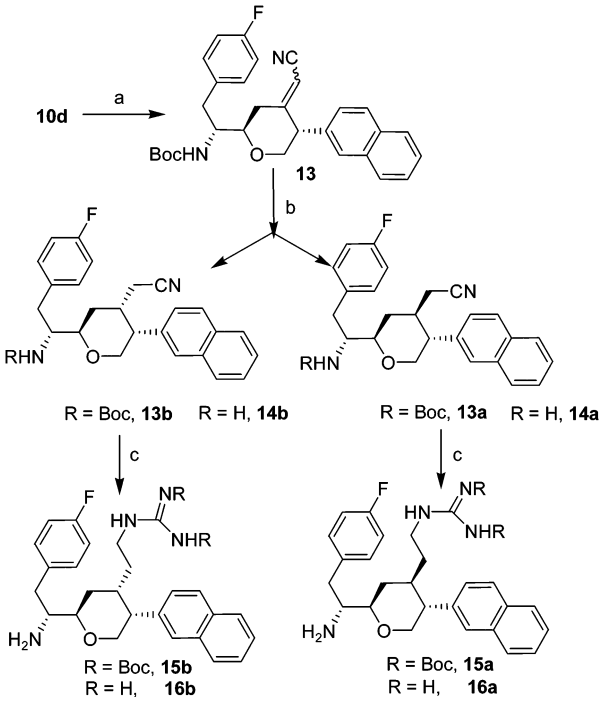
Scheme 4[a]



[a] Reagents and conditions. (a) $(EtO)_2OPCH_2CN$, NaH, THF. (b) H_2, $NaBH_4$, $PdCl_2$, MeOH. (c) (i) H_2, Ni/Ra, MeOH/NH_4OH (1:4); (ii) BocHNC(=NBoc)SMe, $HgCl_2$, Et_3N, DMF; (iii) TFA, DCM.

isomers in a 1:1 ratio. The diastereomers were separated on a silica column. We assigned structure **13b** to the faster moving compounds on the basis of the presence of small coupling values for the signals at about 3.4 ppm. We postulate that this coupling belongs to two equatorial cis protons H-4 and H-5. The NMR spectrum of **13a** shows only large coupling values at this chemical shift, and this should correspond to trans H-4 and H-5 (see expanded spectral regions in Supporting Information). Each diastereoisomer was carried out separately through the next steps, giving **16a** and **16b**.

The results in Table 2 show the results of in vitro testing 2,4,5-trisubstituted tetrahydropyrane analogues for binding and functional activity at MC4R in the cell-based assays. Compared to the model tripeptide H-DPhe-Arg-Trp-NH_2, **12c** is a weak partial agonist as judged by EC_{50} and E_{max} values. On the other hand, **16a** and **16b** bind to MC4R with somewhat lower potency than the tetrapeptide but do not trigger the functional response of the receptor.

Table 2. Biological Activity of Selected Tetrahydropyran Analogues at the Melanocortin Receptor-4 (MC4R)[a]

compd	K_i [nM]	EC_{50} [nM], (E_{max} [%])
H-DPhe-Arg-Trp-NH_2	1188	2803 (49)
12a	>25 000	>50 000 (0)
12b	>25 000	>50 000 (0)
12c	9930	9235 (32)
14a	>25 000	>50 000 (0)
14b	>25 000	>50 000 (0)
16a	2801	>50 000 (0)
16b	4960	>50 000 (0)

[a] For assay procedures, see Supporting Information.

In view of the recent report about the existence of nonspecific interactions in the biological assay mixtures, resulting in the discovery of "artificial" hits,[29] it may be important to address this question whenever novel actives are found that deviate significantly from the established and validated ligands. In our case, compounds **12a**, and in particular **12b**, are structurally close to **12c** but do not show any activity at MC4R. Furthermore, significantly increased receptor binding occurs with **16a** and **16b** upon transformation of the cyano group of **14a** and **14b** into a hydrophilic guanidine functionality. These results argue against the possibility that potential effects of nonspecific association bias the screening results in this class of compounds. It should also be pointed out that comparison of both binding and functional response in the cellular assays involving G-protein-coupled receptors limits the possibility of nonspecific interactions and, therefore, is less likely to produce artifacts than the enzyme inhibition assays.

Our data indicate that this peptidomimetic design based on the 2,4,5-trisubstituted tetrahydropyrane structures can indeed lead to the biologically active molecules. Presumably, this scaffold meets some of the conformational requirements of the melanocortin receptors. This approach allows for significant departure from analogues with peptidic character and is amenable to diastereoselective synthesis from readily available materials.

Supporting Information Available: Experimental details and characterization of compounds as well as biological assay procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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