Studies toward a Library of Tetrahydrofurans: Click and MCR Products of Mono- And Bis-Tetrahydrofurans

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Libraries of novel low molecular weight compounds with unique structural features and unknown properties have found a wide range of applications in "hit to lead" screening and drug development programs. Hundreds of thousands of compounds are already available to screening centers in industry and, more recently, in academia. Yet, new compounds with novel skeletons that could lead to new biological properties and expand the intellectual properties (IP) frontiers are always desirable. With this goal, we prepared a library of mono- and bis-tetrahydrofuran derivatives substituted with unusual fragments, such as **I** and **II** (Figure 1). These compounds, which can have as many as sixteen stereoisomers, feature a cyclic ether segment similar to the naturally occurring Annonaceous acetogenins,[1] such as solamin, **1**, or asimicin, **2**. The latter compounds are known for a wide range of biological activities, including anticancer properties. They are among the most powerful inhibitors of complex I (NADH/ubiquinone oxidoreductase) in the mitochondrial transport systems.[1,2] They also bind strongly to Ca^{2+}.[3] The THF rings in these compounds are essential for high anticancer activities,[4] as well as complexation to Ca^{2+}. Since intramitochondrial Ca^{2+} ions control both the rate of ATP production by oxidative phosphorylation and the induction of the mitochondrial permeability transition (MPT),[5] both mono- and bis-THF compounds could modulate these processes.

We argued that the mono- and adjacent bis-THF acetogenins could be modified with unnatural side chains providing hybrid structures located in new chemical space. Such compounds could have functions that could be unknown and entirely different than a naturally occurring acetogenin, and could be determined using high-throughput screening (HTS). Thus, we focused on compounds having heterocyclic scaffolds that could be prepared readily using clickable processes, such as the Sharpless alkyne−azide Click reaction[6] and Ugi and Biginelli MCRs.[7] These reactions were previously found suitable for library synthesis. Before embarking on the synthesis of a large series of structurally and stereochemically diverse mono- and bis-THF compounds, we decided to carry out model studies by synthesizing a small library of THF compounds substituted with triazole, urea, dihydropyrimidine, and dipeptide fragments. These were prepared from several *trans*-mono-THF alcohols, and one each of the enantiomerically pure *trans*-mono-THF and *cis,threo,cis*-bis-THF diols (*vide infra*) by using the alkyne−azide coupling reaction and Ugi and Biginelli MCRs. In this Report, we describe the synthesis of both symmetrically and unsymmetrically disposed molecules as examples to highlight our initial studies.

As shown in Figure 1, a symmetrical mono-THF compound of the general structure **Ia** has three stereoisomers, two trans and one cis compound, analogous to the mono-THF diols **3**, whereas a unsymmetrical mono-THF compound, **Ib**, has four stereoisomers, two trans and two cis compounds. Similarly, the symmetrical and unsymmetrical bis-THF derivatives **IIa** and **IIb** have ten and sixteen stereoisomeric structures, respectively. All of these target structures could be prepared using appropriately functionalized THF and bis-THF precursors. At first, we focused on the synthesis of the symmetrical mono- and bis-THF compounds **Ia** and **IIa**, substituted with triazole fragments. The latter were readily prepared by an azide−alkyne Click reaction, an easy and efficient way of increasing the diversity of a chemical library. This reaction is highly selective and takes place under mild conditions. It is orthogonal to most

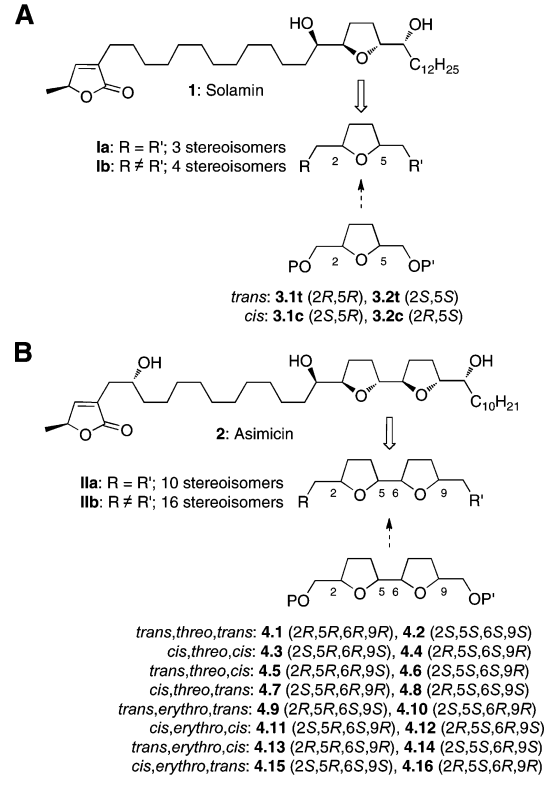

Figure 1. Mono-THF and bis-THF compounds based on the mono-THF and bis-THF acetogenins, solamin and asimicin, and their precursors. For the mono- and bis-THF diols **3** and **4**: P = P′ = H, and for the monobenzoate of compound **4**, P = Bz and P′ = H.

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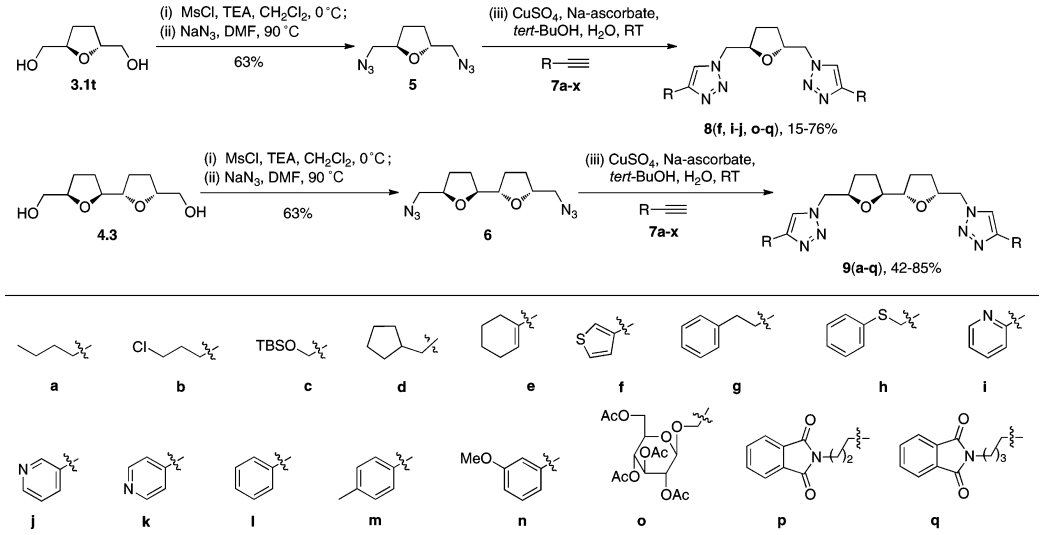
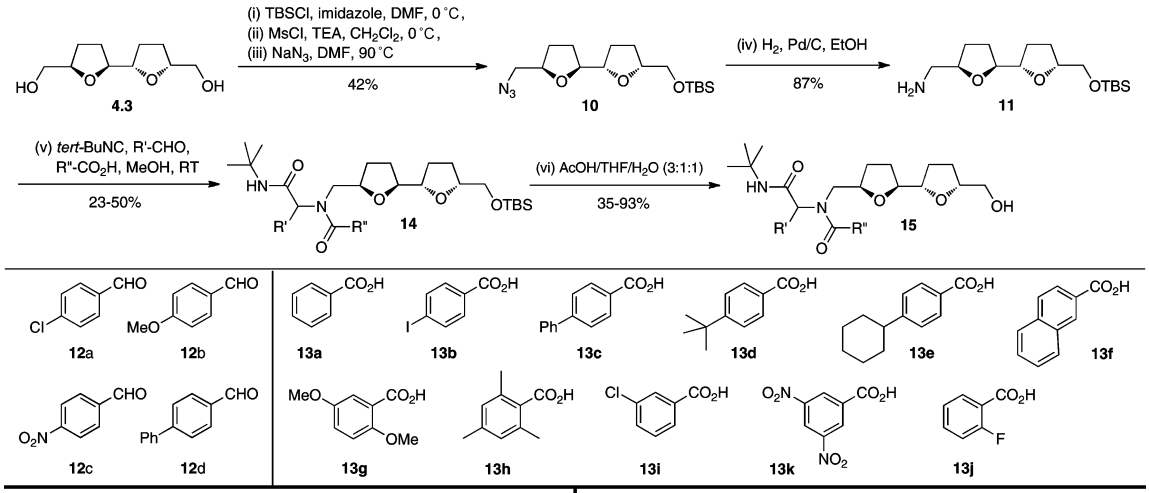


Figure 2. Synthesis of mono- and bis-THF triazole libraries via key bis-azides.

chemical and biochemical transformations, and therefore it has also found frequent applications in bioconjugation.[8] We prepared *trans*-**Ia** and *cis-threo-cis*-**IIa** using the mono- and bis-THF diazides **5** and **6**, respectively, and a series of alkynes (Figure 2). Thus, the diazides **5** and **6** were synthesized using the previously described mono- and bis-THF diols **3.1t** and **4.3** in two steps,[2] including mesylation of the diols using MsCl to give the dimesylates, followed by substitution with NaN_3. The reaction between the alkynes and azides was next conducted using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate to give the mono- and bis-THF triazole hybrid molecules in unoptimized 15−85% yield.

Next, we focused on the Ugi four-component MCR, which can afford a wide variety of compounds quickly in a single step from appropriately functionalized mono- or bis-THF amines (or aldehydes) and commercially available aldehydes (or amines), isocyanides, and carboxylic acids. In this reaction, a protected dipeptide is formed through the initial formation of the imine intermediate by a reaction between an aldehyde and an amine, which is followed by a reaction with the isocyanide and the carboxylic acid. Presumably, MCR reactions could be conducted on both side chains of the THF rings in compounds **3** or **4**, which would give symmetrical compounds; here, we focused on unsymmetrical compounds that could be obtained by performing these reactions on only one side chain of the molecules. While these two alternatives would increase the chemical space, we restricted our activity to unsymmetrical compounds since they are less complicated and obtained in higher yields than the symmetrical compounds. Thus, we carried out this process using a mono TBS-protected bis-THF-amino alcohol, **11**, which was prepared from the bis-THF diol **4.3** via azide **10** (Figure 3). First, diol **4.3** was converted to azide **10** in three steps, including monoprotection of the diol using



Number	Aldehyde (R'-CHO)	Acid (R"-CO_2H)	Product **14**'s (Yield)	Product **15**'s (Yield)	Number	Aldehyde (R'-CHO)	Acid (R"-CO_2H)	Product **14**'s (Yield)	Product **15**'s (Yield)
1	**12a**	**13a**	**14.1** (50%)	**15.1** (77%)	8	**12d**	**13e**	**14.8** (44%)	**15.8** (93%)
2	**12b**	**13a**	**14.2** (54%)	**15.2** (74%)	9	**12d**	**13f**	**14.9** (43%)	**15.9** (82%)
3	**12c**	**13a**	**14.3** (23%)	**15.3** (67%)	10	**12d**	**13g**	**14.10** (47%)	**15.10** (80%)
4	**12d**	**13a**	**14.4** (49%)	**15.4** (35%)	11	**12d**	**13h**	**14.11** (49%)	**15.11** (49%)
5	**12d**	**13b**	**14.5** (40%)	**15.5** (80%)	12	**12d**	**13i**	**14.12** (35%)	**15.12** (76%)
6	**12d**	**13c**	**14.6** (41%)	**15.6** (62%)	13	**12d**	**13j**	**14.13** (41%)	**15.13** (41%)
7	**12d**	**13d**	**14.7** (47%)	**15.7** (71%)	14	**12d**	**13k**	**14.14** (42%)	**15.14** (93%)

Figure 3. Synthesis of Ugi products using bis-THF diol **4.3** via bis-THF amine **11**.

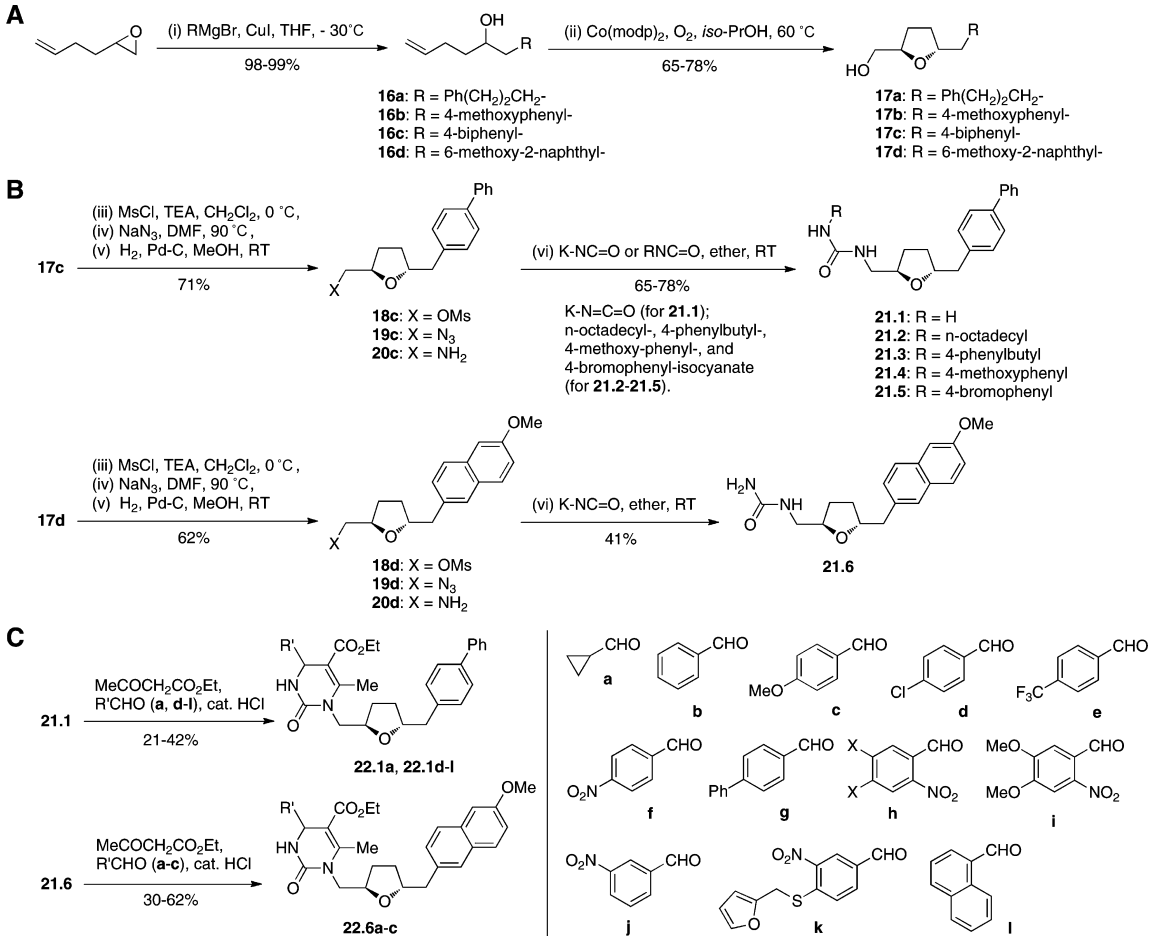


Figure 4. Synthesis of the (A) mono-THF methylamines via $Co(modp)_2$-catalyzed oxidative cyclization (Co-OC) reaction, (B) the urea derivatives for the Biginelli reactions, and (C) the dihydropyrimidinones obtained in the Biginelli reaction.

TBSCl, mesylation of the resulting mono TBS-protected bis-THF diol, followed by substitution of the mesylate using NaN_3, as used earlier for the conversion of **3.1t** and **4.3** to **5** and **6**. Subsequently, azide **10** was hydrogenated in the presence of 10% Pd/C to give amine **11** in 87% yield (crude) that was used in the Ugi reaction without further purification. As shown in Figure 3, amine **11** was reacted with *tert*-BuNC as the isonitrile component and a series of aldehydes, **12**, and carboxylic acids, **13**, giving the Ugi products **14**. TBS deprotection of compounds **14** afforded **15**. In a typical reaction, aldehyde (1 equiv), acid (1 equiv), and *tert*-BuNC (1 equiv) were added sequentially to a solution of the amine **11** (1 equiv) in methanol, and the reaction mixture was stirred at room temperature for 12−24 h. After completion of the reaction (monitored by TLC), the solvents were removed and workup utilized water and EtOAC. Pure Ugi products, **14**, were obtained after chromatography on SiO_2 in 23−54% yield. The TBS group in these compounds was deprotected using 60% AcOH in a 1:1 mixture of THF/water, giving the TBS-free Ugi products **15** in 35−93% yield (unoptimized). As shown in Figure 3, the diversity of the bis-THF library could be easily increased by using a wide array of isonitriles, aldehydes and acids, thereby enhancing the probability of a hit in the biological screens.

For the THF-based Biginelli MCR products, we prepared urea derivatives using a series of readily available mono-THF amines **20**, which were synthesized starting with 1,2-epoxyhexene via the bishomoallylic alcohols **16** and mono-THF alcohols **17** (Figure 4A). Thus, bis-homoallylic alcohols **16a**−**16d** were readily obtained by the CuI-catalyzed opening of the epoxide using an appropriate alkyl- or arylmagnesium bromide, including *n*-nonyl-, 3-phenylpropyl-, 4-methoxyphenyl-, 1,4-biphenyl-, and 6-methoxy-2-naphthylmagnesium bromide, respectively, and converted to the mono-THF alcohols **17a**−**17d** using the $Co(modp)_2$-catalyzed oxidative cyclization (Co-OC) reaction.[9] We used alcohols **17c** and **17d** in subsequent reactions and converted them to amines **20c** and **20d** in three steps: the primary hydroxyl functions in **17c** and **17d** were mesylated; the resulting mesylate products **18c** and **18d** were reacted with NaN_3 to give azides **19c** and **19d**, and the latter products were hydrogenated in the presence of Pd−C to give the desired amines in 71% and 62%, respectively.

Amine **20c** was reacted with several alkyl- or aryl isocyanates, such as *n*-octadecyl-, 4-phenylbutyl-, 4-methoxyphenyl-, and 4-bromophenyl-isocyanate, giving the unsymmetrical urea derivatives **21.2**−**21.5**, respectively (Figure 4B). Both amines **20c** and **20d** were reacted with potassium isocyanate to produce compounds **21.1** and **21.6** in 34% and 41% yield (unoptimized), respectively, and these derivatives were used for the synthesis of numerous Biginelli products. All urea compounds were obtained as colorless solids after the crude products were washed multiple times with CH_2Cl_2, and the yields refer to the solid materials.

In the Biginelli reaction,[10] a β-keto ester and an aldehyde react with an urea to give the corresponding 3,4-dihydropyrimidin-2(1H)-one derivatives. Thus, compounds **21.1** and **21.6** were reacted with ethyl acetoacetate and a series of aldehydes under acidic conditions, affording the cyclic urea derivatives **22** (Figure 4C). Of course, all compounds were obtained as a mixture of the diastereomeric products at the newly generated stereogenic center.

The azide−alkyne Click reaction and the Ugi and Biginelli MCRs offer rapid access to libraries of non-natural compounds that are highly complex and otherwise inaccessible or difficult to synthesize. While the azide−alkyne Click reaction provides the triazole derivatives in high yield, Ugi and Biginelli MCRs provide access to compounds that have higher orders of complexity. Here, by using mono- and bis-THF rings, as well as both symmetrical and unsymmetrical intermediates, as the next set of starting materials, one can increase not only the number of new chemical libraries, but also their complexities and overall shape, simply by changing the relative stereochemistry of the THF rings. For one set of compounds, there can be four sets of stereoisomeric products in a mono-THF library, and as many as sixteen sets for a bis-THF library.[11] Because the mono-THF and bis-THF compounds, as well as some nitrogen analogs and higher-order THF rings, can be readily obtained starting with the all-carbon skeletons, and using numerous oxidative processes, including the Re(VII),[12] Co(II), Os(VIII),[13] and Ru(VIII)[14] oxide-mediated/catalyzed OC reactions, this approach offers opportunities for the design and synthesis of an unprecedented set of non-natural compounds by the combination with Click and MCR reactions. Presumably, the THF-based chemical space can be further increased by introducing additional substitution on the THF rings and adding new synthetic transformations. Such isomeric compound libraries can demonstrate novel biological properties, which can be determined through high-throughput screening (HTS).

An efficient synthetic approach was developed for the construction of a new class of tetrahydrofuran-based hybrid molecules using the Sharpless azide−alkyne Click reaction and the Ugi and Biginelli MCRs as key transformations. Numerous mono- and bis-tetrahydrofuran triazoles, peptides, and acyclic and cyclic urea derivatives with diverse structural features were prepared in fair to good yields from the readily available mono- and bis-tetrahydrofuranyl azides and amines. Selected compounds have been submitted for evaluation under the MLSCN/MLPCN programs.[15]

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Supporting Information Available. Details of experimental procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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