

1,2-Difunctionalized Bicyclo[1.1.1]pentanes: Long Sought After Bioisosteres for *ortho/meta*-Substituted Arenes

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Abstract: The development of a versatile platform for the synthesis of 1,2-difunctionalized bicyclo[1.1.1]pentanes to potentially mimic *ortho/meta*-substituted arenes is described. The synthesis of useful building blocks bearing alcohol, amine, and carboxylic acid functional handles has been achieved from a simple common intermediate. Several *ortho* and/or *meta*-substituted benzene analogues as well as simple molecular matched pairs have also been prepared using this platform. In-depth biological and computational studies are currently in progress to validate the *ortho* and/or *meta*-character of these new bioisosteres. Results of these investigations will be reported in due course.

Main text: Over the past decade, medicinal chemist's mission to "escape from flatland" has altered the way synthesis in drug discovery is conducted.¹ Specifically, C(sp³)-rich structures, where the venerable benzene ring is replaced with saturated bioisosteres, have started to rapidly populate the patent literature, compound libraries, and the toolbox of medicinal chemistry tactics.¹ These 3D-moieties often exhibit improved biological activities, physicochemical properties and metabolic profiles compared to the parent benzene ring.² These singular characteristics have encouraged several academic and industrial groups, including the Pfizer/Scripps team, to achieve the functionalization of these small structures.³ As a subset of these bioisosteres,

bicyclo[1.1.1]pentane (BCP) cores have been extensively studied and proven valuable alternatives to benzene rings.³ However, a quick search into the literature highlights that only bridgehead functionalizations, mimicking para-substitution of the benzene ring, have been reported to date (Figure 1A). This is certainly due to the absence of synthetic methods to achieve 1,2-difunctionalization of BCPs rather than the lack of desire to replace *ortho*- and/or *meta*-disubstituted benzenes in bioactive molecules which has been regularly mentioned over the years.² Recently, Mykhailiuk and co-workers reported the synthesis of bicyclo[2.1.1]hexanes as the first example of saturated bioisosteres of *ortho*-disubstituted benzenes.⁴ Conversely, there is still a gap in the literature for the synthesis of 1,2-difunctionalized BCP skeletons that would act as *ortho*- and/or *meta*-disubstituted benzenes (Figure 1B). Our foray into the synthesis of such compounds started with a directed C-H activation strategy where a bridgehead amide direction group was installed to activate the side position of the BCP. Unfortunately, all efforts towards this directed approach proved unsuccessful. While trying other tactics, we came across a paper published by the group of Schliiter in 1995.⁵ In their report, the authors synthesized the [1.1.1]propellane **1** bearing a methoxy methyl (MOM) protected hydroxyl group in the side chain.⁵ Inspired by this unexplored precedent and capitalizing on newly emerging methods for the cross-coupling of previously unreactive carboxylic acids (via decarboxylative functionalization) we report herein the development of a platform to synthesize 1,2-difunctionalized bicyclo[1.1.1]pentanes from compound **2** (Figure 1C), synthesized from **1** in 3 steps.

Figure 2 highlights the preparation of several key building blocks that allow for the preparation of various 1,2-difunctionalized BCP skeletons. Towards this end, our studies commenced by optimizing Schliiter's synthetic sequence leading to compound **1** which was obtained in 36% yield over 5 steps (Figure 2A). With compound **1** in hand, building block **2** was easily prepared in 3 steps through radical difunctionalization,^{3d} deiodination,^{3d} and chlorine-acetate exchange (18% overall yield, Figure 2B). Compound **2** was chosen for the synthetic versatility it offers. Indeed, alcohol **3**, carboxylic acid **4**, and amine **5** were easily obtained from **2** in one, two, or three steps, respectively (Figure 2C) via simple functional group manipulation. Finally, functionalization the [1.1.1]propellane **1** side chain was undertaken (Figure 2D). Radical ring opening and dehalogenation of **1** afforded compound **6** which was directly deprotected and oxidized to afford carboxylic acid **7** in 18% yield over 4 steps. The carboxylic acid moiety was the adequate handle to prepare redox active ester **8** and test its ability to undergo decarboxylative transformations. Pleasingly, compound **8** delivered borylated compound **9** in satisfactory yield under our reported

copper-catalyzed decarboxylative borylation conditions.⁶ It is worth noting that compounds **8** and **9** offer limitless possibilities regarding the preparation of medicinal chemistry relevant structures. The synthesis of these 1,2-difunctionalized bicyclo[1.1.1]pentane building blocks encouraged us to examine the practicality of the platform in the context of preparing drug bioisosteres as outlined in Figure 3.

The synthesis of Sonidegib bioisostere **10** was first investigated. Starting from compound **2**, MOM deprotection, followed by alcohol oxidation and ester formation afforded redox active ester **11** in 74% yield (Figure 3A). Subsequent decarboxylative Negishi arylation successfully delivered compound **12** in good yield.⁷ Finally, a simple deprotection/oxidation sequence followed by amide bond formation afforded Sonidegib bioisostere **10**. A similar strategy was employed to synthesize Lomitapide bioisostere **13** from redox active ester **11** demonstrating the flexibility of the 1,2-difunctionalized bicyclo[1.1.1]pentane platform (Figure 3A). Efforts then turned to the synthesis of Boscalide bioisostere **14** which bears an amide at the bridgehead position (Figure 3B). Starting from alcohol **3**, a 5-step sequence afforded redox active ester **15** which smoothly underwent decarboxylative Negishi arylation to afford intermediate **16**. Then, ester hydrolysis followed by Curtius rearrangement and carbamate deprotection gave the amine compound **17** in 70% yield. Final amide bond formation delivered the desired Boscalide bioisostere **14**. Lastly, the versatility of the platform was demonstrated by the synthesis of Meclizine bioisosteres **18** and its reversed analog **19** (Figure 3C). From **3**, a simple 4 step sequence (protection – reduction – deprotection – protection) afforded intermediate **20** bearing the methyl group at the bridgehead position. The same steps were repeated in a different order from compound **2** to afford intermediate **21** (reversed of **20**) which bears the methyl group at the side chain position. Both intermediates **20** and **21** underwent amide bond coupling to obtain Meclizine bioisosteres **18** and **19** in 45% and 41% overall yield, respectively.

The scope of the 1,2-difunctionalized bicyclo[1.1.1]pentane platform was further expanded as outlined in Figure 4. Thus, compounds **22** and its reversed analog **23** were synthesized as bioisosteres of Phthalylsulfathiazole in 7 steps (34% and 21% overall yield) from **2** (Figure 4A). In addition, compounds **24** and **25**, bioisosteres of Tolvaptan, were targeted and can provide access to a total of 4 compounds to study (after separation of the diastereomers and supercritical fluid chromatography (SFC) separation of enantiomers) due to the presence of an additional chiral center (Figure 4B). Finally, a molecular matched pair synthetic campaign was undertaken to

evaluate the usefulness of the new platform in the context of fragment-based approach (Figure 4C). Compound **26**, **27**, and **28** were therefore synthesized from **2**, **3**, and **1** in 7, 6, and 6 steps, respectively. Those simple fragments are being evaluated and should deliver precious information regarding the *ortho* and/or *meta*-character of the 1,2-difunctionalized bicyclo[1.1.1]pentane derivatives.

All of the compounds presented above are now being separated via SFC to isolate both enantiomers. Biological and computational studies are underway to validate the *ortho* and/or *meta*-character of all the aforementioned bioisosteres and results will be reported in due course.

Conclusion: For years, chemists in both industry and academia have been focusing on the incorporation of the bicyclo[1.1.1]pentane skeletons that mimic *para*-substituted benzenes. Herein, we reported the development of an useful platform that answers the long-standing challenge of accessing 1,2-difunctionalized bicyclo[1.1.1]pentane building blocks that could serve as *ortho* and/or *meta*-substituted benzene analogues. While the approach is admittedly lengthy, the key intermediates from which divergent synthesis can take place are easily accessed on scale and amenable to outsourcing. Future studies on more simplified access to such compounds will be pursued based on biological findings. As described above, several bioisosteres of *ortho/meta* disubstituted benzene containing drugs as well as simple benzene molecular matched pairs were obtained using this methodology. This initial disclosure is presented with urgency due to the demand in industry for routes to such molecules. Focus internally remains now on the biological and computational analysis of these new compounds and these results will be disclosed in due course. In the meanwhile the synthetic route delineated herein will likely be of high interest to those working in the fields of organic synthesis, agrochemistry, and/or medicinal chemistry.

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Figures:

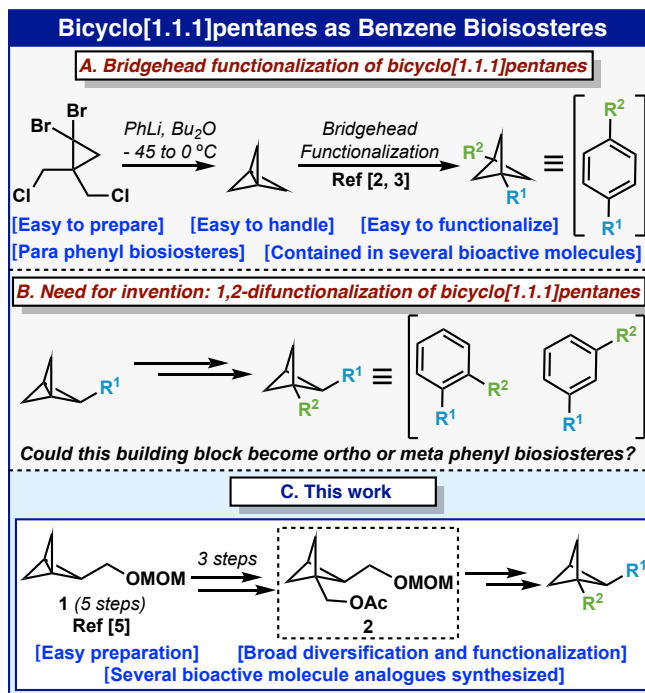


Figure 1. Introduction to bicyclo[1.1.1]pentanes as arene bioisosteres

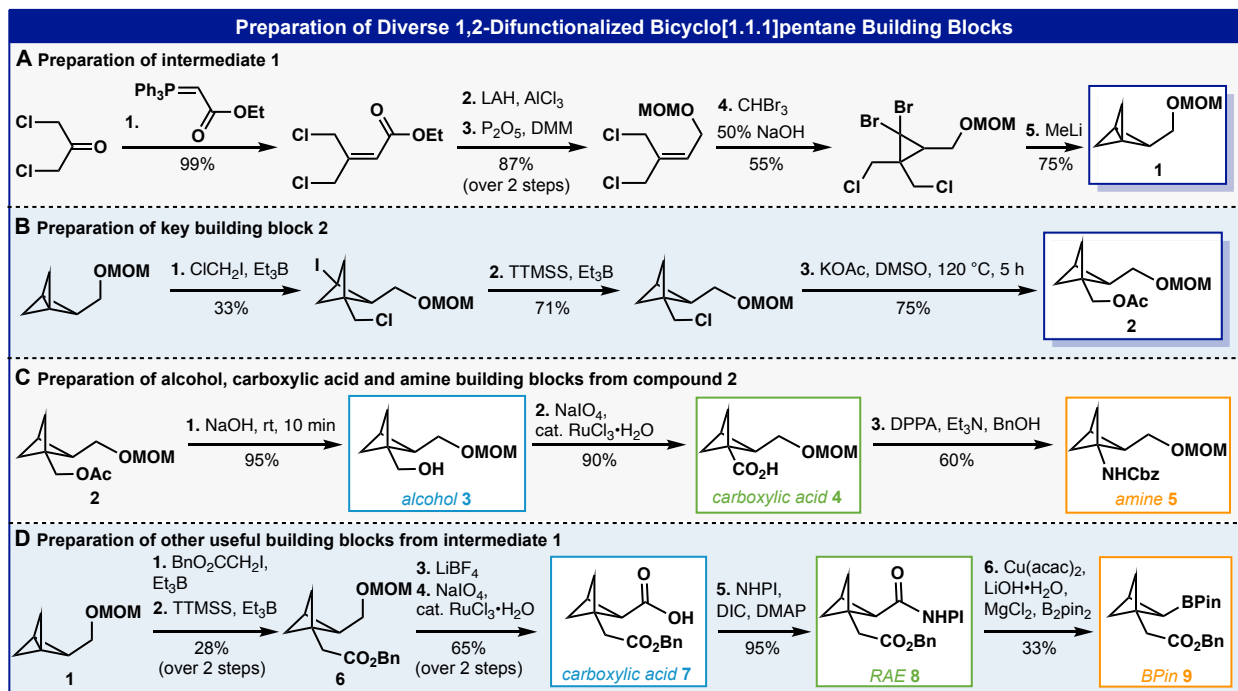


Figure 2. Preparation of diverse 1,2-difunctionalized bicyclo[1.1.1]pentane building blocks.

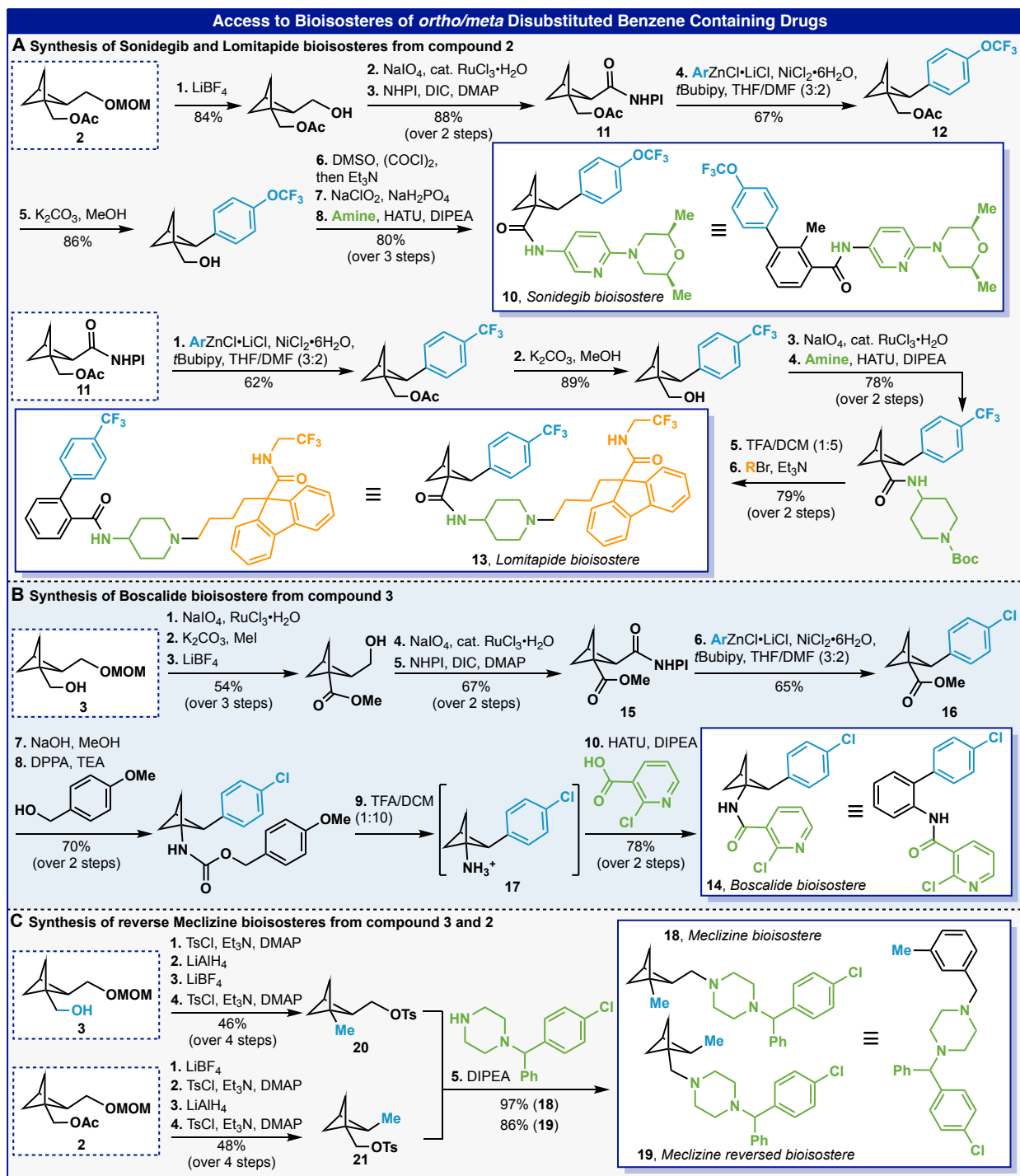


Figure 3. Access to bioisosteres of *ortho/meta* disubstituted arene containing drugs.

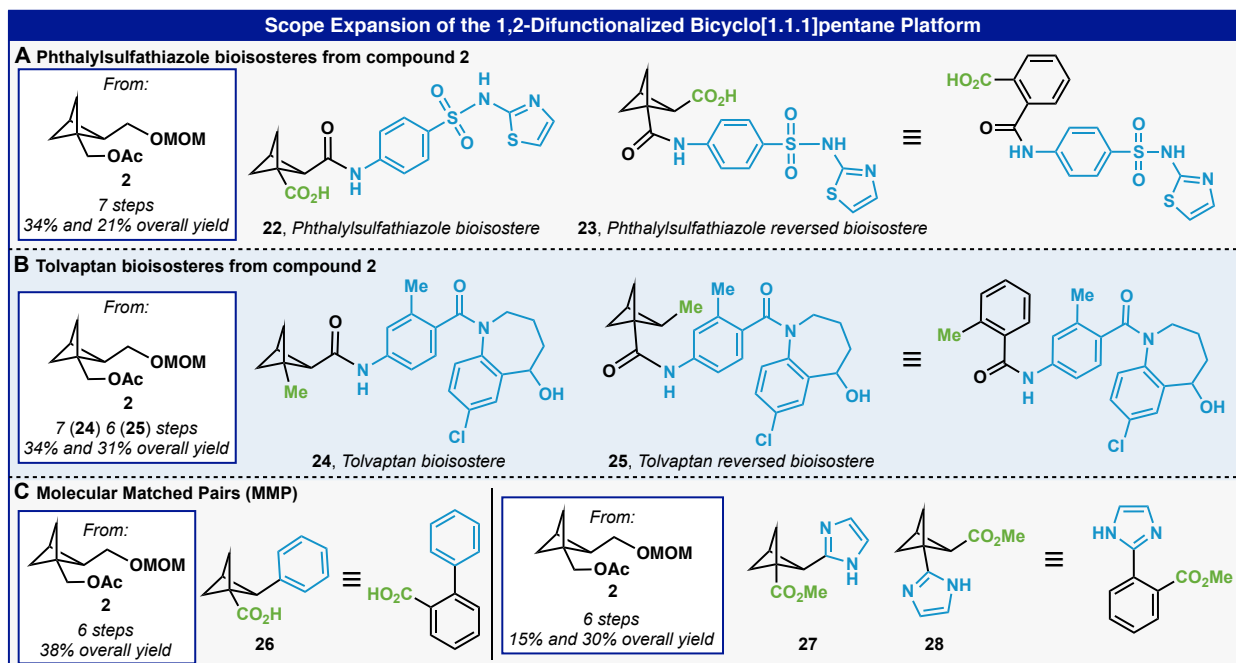


Figure 4. Scope expansion of the 1,2-difunctionalized bicyclo[1.1.1]pentane platform.