Stellane at the Forefront: Derivatization and Reactivity Studies of a Promising Saturated Bioisostere of ortho-Substituted Benzenes

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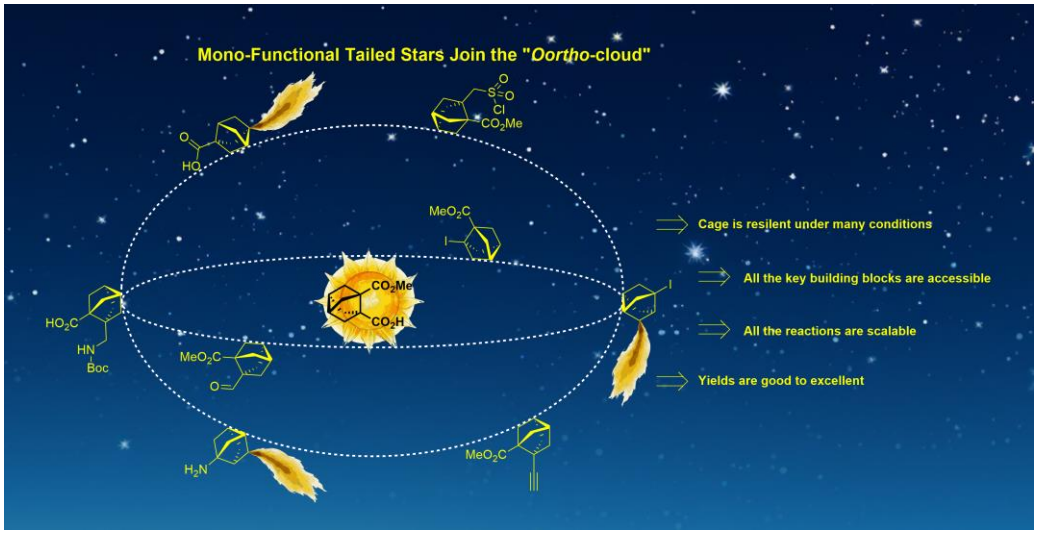
Supporting Information Placeholder



ABSTRACT: This work highlights stellane's cage stability and derivatization opportunities. Using modern synthesis protocols, a diverse range of building blocks were synthesized. Stellane's reactivity and chemical tolerance were rigorously evaluated across different reaction systems, demonstrating its promise as a bio-isosteric scaffold. It can be utilized in scaffold-based molecular design and offers topological precision superiority over existing *ortho*-isosteres, as well as mono-substituted benzene mimetics, holding the potential to become a robust platform for future medicinal chemistry studies.

In medicinal chemistry, bio-isosteres are instruments in developing drugs with improved therapeutic efficacy and reduced adverse effects[1-3]. Notably, *para*-benzene isosteres[4-6] have been a focal point of investigation, with cores like bicyclo[1.1.1]pentane[7-10], bicyclo[2.2.2]octane[5-6, 10], and cubane[4, 10-13] exhibiting significant promise in deriving pharmacologically active compounds. Despite their longstanding discovery[14-17], the allure of these cores endures, as reflected by a rich array of studies in eminent journals, exploring their functionalization, scalable synthesis, and broad property range[8-10, 12-13, 18-32].

The current landscape of the *ortho*-benzene isosteres is full of viable options at the first glance (**Figure 1, A-E**)[18, 33-36], however if we look closer, it becomes evident, that the candidate-cores are either poorly accessible synthetically (**Figure 1, D-E**)[18, 36], or remain heavily underexplored, due to their very recent introduction to the field (**Figure 1, A-B**)[33-34]. In this regard it is safe to say that transitioning from *para*- to *ortho*-substituted frameworks, the scientific community encounters a scarcity of structurally compact and versatile scaffolds[6, 13, 18, 34] akin to the well-established para- and mono-substituted benzene isosteres[1, 6, 15, 17, 37-40]. This gap accentuates the exigency for novel scaffolds that could parallel the *ortho*-substituted benzene derived bioactive compounds while providing a conducive platform for affordable functionalization and derivatization. Among the known *ortho*-benzene isosteres, saturated 3-dimensional hydrocarbons derivatives like bicyclo[2.1.1]hexanes have been synthesized[23, 41-43] and validated[33-34], offering promising cores for bioactive compounds such as Valsartan, Boskalid, and Fluxapyroxad analogues. Furthermore, the synthesis of bicyclo[2.1.1]hexanes has established a precedent

in creating saturated bioisosteres for *ortho*-disubstituted benzenes *de novo*, paving the way for further exploration in this domain. However, despite these advancements, the quest for the ideal *ortho*-benzene isostere that encompasses both structural compactness and broad options for functionalization continues. The emerging scaffold, Stellane[44-45], stands as a noteworthy candidate in this pursuit, promising a fusion of bio-isosteric potential with a robust framework for diverse derivatization. Stellane (bisnoradamantane), emerging as a 1,5-disubstituted motif through modern synthesis protocols[45], spearheads the exploration of *ortho*-isosteric scaffolds. Its compact C8 high *Fsp*^{3}- 3-dimensional cage precisely aligns geometrically with *ortho*-substituted benzene[45], expanding the bio-isosteric frontier. This robust scaffold, when juxtaposed with existing *ortho*-isosteres, unfolds a superior avenue for diversifying 1,5-disubstituted building blocks. Separately, the allure of synthesizing mono-functional Stellanes, though not *ortho*-benzene bioisosters, holds promise in medicinal chemistry, leveraging the stellane core's benefits. The quest to understand stellane's chemical behavior in various reaction conditions and chemical environments, seeks to find answer, whether it resembles the resilience of adamantane or the lability of cubane[13, 39, 46], and invites a rich exploration, igniting curiosity on its potential impact in scaffold-based molecular design.

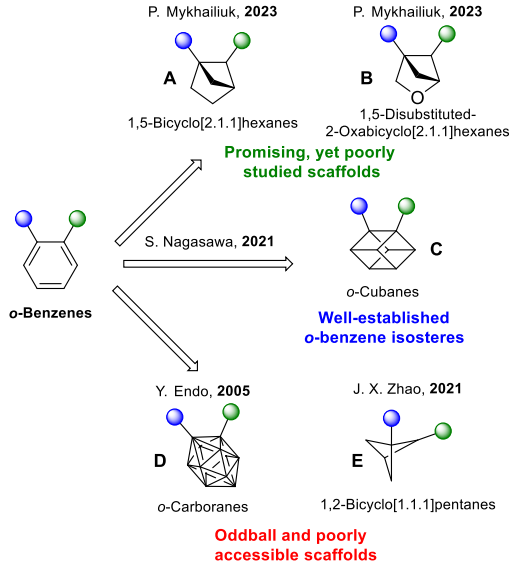
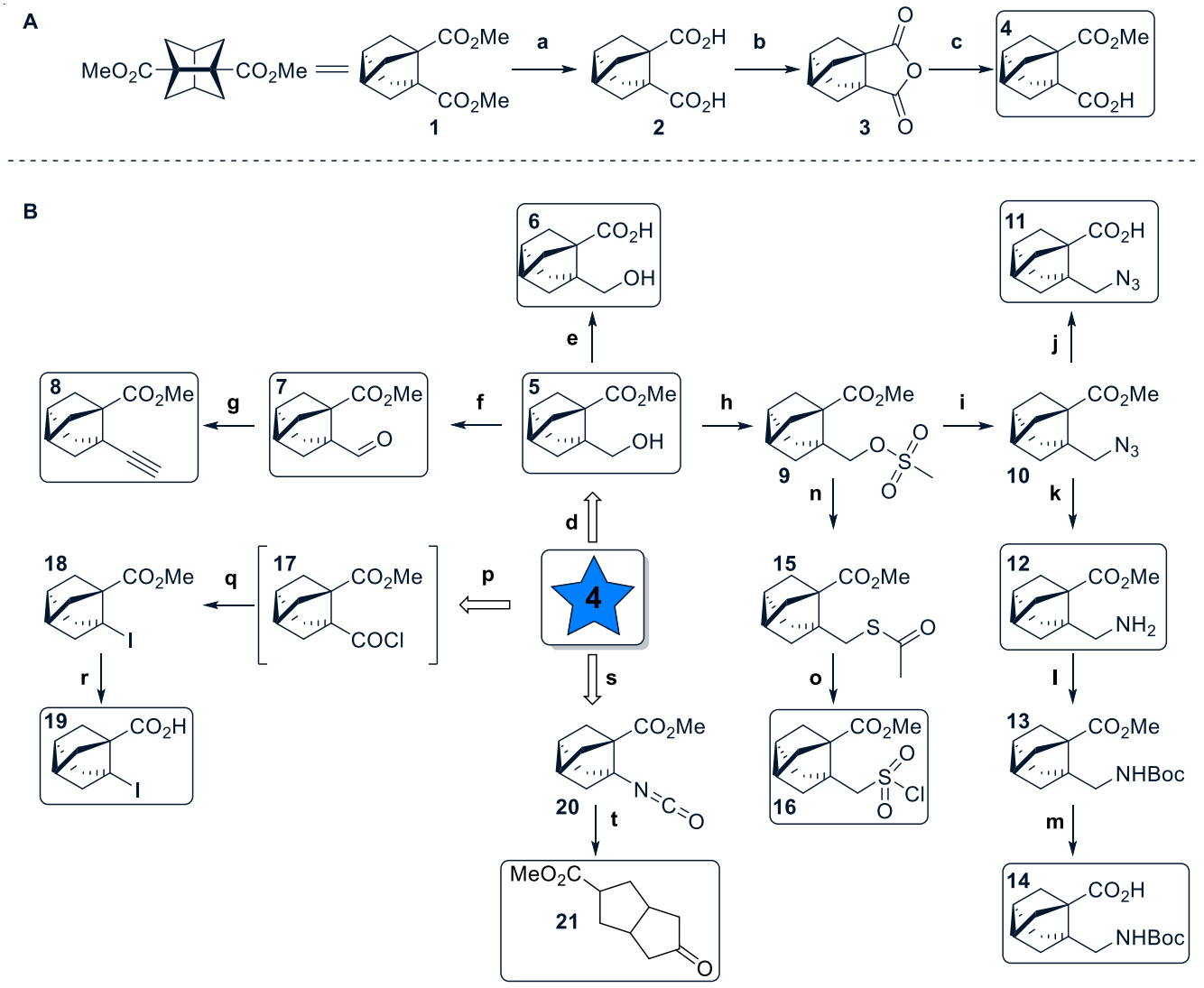


Figure 1. Biologically validated *ortho*-benzene mimetics **A-E**.

Building upon our prior work, where multigram quantities of 1,5-disubstituted stellane were synthesized[45], this study propels forward to exploit this scaffold for creating a diverse array of bifunctional and mono-substituted building blocks. The endeavor encompasses a thorough examination of stellane's reactivity and chemical tolerance across pivotal reaction systems and conditions/interactions with nucleophiles/electrophiles, radical agents, oxidizers/reducing agents, and acids/bases. Through this meticulous pursuit, we aim to seamlessly transition into an in-depth discussion on the findings, potentially spotlighting stellane's forte as a bio-isosteric scaffold and setting the stage for its broader implications in medicinal chemistry.

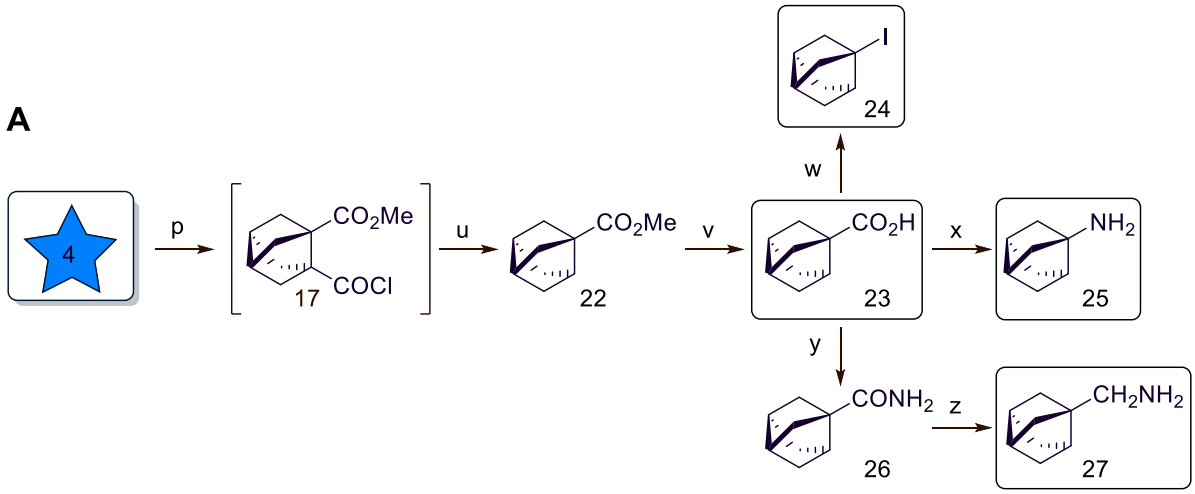
The exploration undertaken in the introductory phase elucidates a substantial limitation in the realm of *ortho*-bioisosteric cores, particularly when it comes to their empirical biological validation. Despite the vast landscape of supposed *ortho*-benzene isosteres[3, 18, 33-35, 41, 47-49], a closer inspection delineates two predominant issues: either the cores are marred by synthetic inaccessibility or they are nascent introductions to the domain, consequently being barely delved into. This scarcity is contrasted with the rich tapestry of established *para*- and mono-substituted benzene isosteres[2-3, 13, 49-51]. The findings underscore a pronounced gap, accentuating the urgency for novel *ortho*-benzene bioisosteric scaffolds that are both structurally compact and amenable to facile derivatization. In this context, even a scaffold presenting a narrow window of chemical modification possibilities stands as a valuable contender. Such a scaffold would not only aid in synthesizing and validating new *ortho*-analogues but also serve as a structural platform, potentially instigating significant advancements in the field of medicinal chemistry. As we tunnel deeper into the results, this discussion endeavors to shed light on the potential of new 1,5-disubstituted stellane core[45] in bridging this evident gap and its consequential impact on future research trajectories. The 1-(methoxycarbonyl)stellane-5-carboxylic acid **4**, synthesized in our prior work[45], aligns conceptually with the extensively investigated 1-(methoxycarbonyl)cubane-4-carboxylic acid[39, 46, 49, 51-52]. This positions it as a central precursor for the synthesis of a potentially broad spectrum of disubstituted stellanes and also offers pathways for exploring mono-functional variants. The foundational 1-(methoxycarbonyl)stellane-5-carboxylic acid **4** was synthesized efficiently through a three-step procedure, starting from the parent 1,5-(dimethoxycarbonyl)stellane **1** (**Scheme 1**). Subsequent modifications involved a selective reduction of the carboxylic group at the 5-th position, followed by a variety of nucleophilic substitutions targeting the methylene group, and decarboxylative substitutions at the 5-th position's carboxylic group (**Scheme 1**). The reduction and nucleophilic substitution route enabled the acquisition of the most important building blocks, including the acid-methylcarbinole **6**, acid-methylene-azide **11**, ether-sulphochloride **16**, acid-aldehyde **7**, ether-acetylene **8**, methyleneamino acid ester **12**, and its *N*-Boc-protected acid counterpart **14** (**Scheme 1**). Meanwhile, the decarboxylation-focused sequence yielded the iodo-acid **19** and the isocyanate **20**. The transformations depicted in **Scheme 1** facilitated the access to both target building blocks and all intermediate products, affording them in good preparative yields and retaining the stellane core intact. Notably, attempts to react **20** with alcohols (*tret*-butanol, or methanol) left the starting isocyanate intact even after 72 h reflux. At the same time acidic hydrolysis of **20** was also unsuccessful due to the inherent push-pull instability[53-55] of the substrate, leading to immediate Grob-type fragmentation,[56-57] which yielded ketoester **21** as a mixture of two diastereomers. The synthesized building blocks serve as promising precursors for creating a diverse set of *ortho*-benzene analogs with potential biological activity. Furthermore, they can serve as compact, structurally rigid core building blocks suitable for both conventional combinatorial and DNA-encoded chemistry[58] approaches.



C

Experimental conditions: ***a)*** *MeOH/H_2O/NaOH r.t., overnight; MeOH/HCl/EtoAc, 87.5% yield;* ***b)*** *Ac_2O, 3h reflux; evaporation, crystallization CCl_4, 84.9% yield;* ***c)*** *MeONa/MeOH, 3h, 60 ^oC; H_2O/MtBE/HCl, 85.6% yield;* ***d)*** *THF/CDI, 2h, 50 ^oC, $NaBH_4$/H_2O, 2h, 0-10 ^oC, 78% yield;* ***e)*** *MeOH/NaOH, 24h, 40 ^oC; H_2O/$NaHSO_4$ (pH = 2), MTBE, yield 99%;* ***f)*** *DCM/PCC, 3h, 0-25 ^oC, 67,2% yield;* ***g)*** *MeOH/K_2CO_3/dimethyl (1-diazo-2-oxopropyl)phosphonate, overnight, 0-25 ^oC, 72% yield;* ***h)*** *DCM/TEA/MsCl, 3h, 0 ^oC, yield 99%;* ***i)*** *DMF/NaN_3/NaI, 48h, 80 ^oC; H_2O, r.t., yield 87.4;* ***j)*** *MeOH/NaOH, 24h, 40 ^oC; H_2O/$NaHSO_4$ (pH = 2), MTBE, yield 88.5%;* ***k)*** *THF/TPP, 2h, 50 ^oC; H_2O, 3h, 50 ^oC; DCM; H_2O/K_2CO_3/MTBE (pH = 12); Dioxane/HCl/MeCN, yield 66.1%;* ***l)*** *DCM/TEA/Boc_2O, 18h, r.t.; H_2O, yield = 99%;* ***m)*** *MeOH/NaOH, 24h, 40 ^oC; H_2O/$NaHSO_4$ (pH = 2), MTBE, yield 99%;* ***n)*** *DMF/Potassium thioacetate/NaI, 72h 80 ^oC; H_2O, yield 87%;* ***o)*** *MeCN/H_2O(4:1)/NCS*HCl(aq), 2h, 0-24 ^oC, yield 78.7%;* ***p)*** *DCM/$C_2O_2Cl_2$/DMF(drop), used without purification;* ***q)*** *DCM/Pyrithione sodium/DMAP/2,2,2-trifluoro iodoethane/hv(200 W, tungsten), 3h, reflux, yield 50%;* ***r)*** *MeOH/NaOH, 24h, 40 ^oC; H_2O/$NaHSO_4$ (pH = 2), MTBE, yield 85.5%;* ***s)*** *Acetone/TEA/EtCF, 0.5 h, -10 ^oC; NaN_3/H_2O, 0.5 h, -10 ^oC; H_2O/Toluene, -10 to -20 ^oC; Toluene, 100 ^oC, 4 h, reflux, yield 88%;* ***t)*** *HCl, reflux, yield 98%.*

Scheme 1. (**A**) Preparation of the key 1-(methoxycarbonyl)stellane-5-carboxylic acid (**4**) and its further derivatization to the most commonly used bifunctional building blocks (**B**). Experimental conditions (**C**). All the potentially valuable building blocks highlighted in brackets. *Detailed procedures are given in the SI.



B

Experimental conditions: u) $CHCl_3$/Pyrithione sodium/DMAP/Ar o.5h, reflux; hv(200 W, tungsten), 0.5h, reflux; 0.1NHCl/CH_2Cl_2/High vacuum (1 mmHg), yield 79.4% v) MeOH/NaOH, 24h, 40 oC; H_2O/$NaHSO_4$ (pH = 2), MTBE, yield 97%; w) DCM/$C_2O_2Cl_2$/DMF(drop), used without purification; DCM/Pyrithione sodium/DMAP/2,2,2-trifluoro iodoethane/hv(200 W, tungsten), 3h, reflux, yield 90%; x) Toluene/TEA/DPPA, 3 h, 100 oC; Toluene/HCl(aq), 4 h, reflux; NaOH(aq)/MTBE, r.t.; Dioxane/HCl, r.t., yield 77%; y) THF/CDI/NH_4OH(aq), r.t., 18h, yield 85.6%; z) THF/$LiAlH_4$, 45 ^oC, 12 h; KOH(aq)/THF, 0 ^oC, 0.5 h; Dioxane/HCl, r.t., yield 90.1%.

Scheme 2. A: Preparation of the mono-substituted stellanes. **B:** Experimental conditions. *Detailed procedures are given in the SI.

The suggested transformations allowed us to synthesize the showcasing set of building blocks, which enable the vast majority of the possible further decoration scenarios, which lead to the potentially bioactive molecules.

Drawing from the 1-(methoxycarbonyl)stellane-5-carboxylic acid **4** and leveraging our prior achievements in decarboxylative substitution (**Scheme 1**), we ventured into the realm of mono-substituted stellanes (**Scheme 2**). This culminated in the synthesis of 1-stellane carboxylic acid (**23**). Through further decarboxylative iodination of this product, we successfully produced 1-iodostellane (**24**). Additionally, employing the Curtius rearrangement technique, we synthesized 1-aminostellane (**27**). All the reactions went smooth and resulted good yields preserving the cage. These endeavors not only attest to the versatility of stellanes but also underscore their potential as valuable scaffolds in the design of novel medicinal chemistry relevant compounds.

The conducted reactions allowed us to access the most important classes of mono-substituted stellanes, like wise acid **23**, amine **27** and iodide **25** (**Scheme 2**) which can be viewed as basic building blocks for further derivatization.

It is noteworthy that while our primary focus was not centered on probing the direct reactivity and the stability of the stellane cage, our investigations provided important insights into its resilience. The stellane core exhibited notable stability across a spectrum of conditions, including but not limited to reduction, oxidation, diverse nucleophilic reactions targeting the methylene group, and decarboxylative substitutions, as well as tolerance to strong acids and bases, underscoring its versatility as a foundational scaffold in medicinal chemistry.

In conclusion, our exploration into the chemistry of Stellanes has highlighted their potential to be a significant addition to the chemical space of medicinal chemistry relevant molecules. Through methodical synthesis and rigorous evaluation, we've expanded the horizons of opportunities for developing novel *ortho*-benzene analogs, highlighting both the versatility and stability of the stellane scaffold. Our successful derivation of a plethora of bi-functional and mono-substituted building blocks showcases stellane's promise as an adaptable core for future molecular designs. The stellane core's resilience against a multitude of chemical conditions further accentuates its geometrical superiority over other *ortho*-isosteres. As we move forward, it's evident that Stellane stands poised to significantly influence the frontier medicinal chemistry, offering a robust platform that bridges current gaps and propels the field to new heights.

ASSOCIATED CONTENT

Supporting Information

The SI contains details of experiments and synthesis; spectral and analytical data for the synthetized compounds; copies of NMR spectra. Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC2252701-2252705.

The Supporting Information is available free of charge on the ACS Publications website.

All information detailed above (SI_BGN_Fin3.pdf)

Video of thermal experiment (ThermalVideo.mp4)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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