Dewar Pyridines: Conformationally Programmable Piperidine Isosteres

Jan Petrovcic,[a] Yaroslav D. Boyko,*[b], Alexander S. Shved,[c] Giovanni Lenardon,[a] Christophe Salome,[d] Quentin Lefebvre,[d] Thomas C. Fessard,*[d] and David Sarlah*[a,c]

[a] Department of Chemistry, University of Pavia, Viale Taramelli 12, 27100, Pavia, Italy
[b] Discovery Chemistry, Merck & Co., Inc., Boston, MA, USA
[c] Department of Chemistry, Carl R. Woese Institute for Genomic Biology, and Cancer Center at Illinois, University of Illinois, Urbana, IL, 61801, USA
[d] SpiroChem AG, Mattenstrasse 22, 4058 Basel, Switzerland

E-mail of corresponding authors: yaroslav.boyko@merck.com, thomas.fessard@spirochem.com, sarlah@illinois.edu

Abstract. *Bioisosteric replacement is an indispensable tool in the medicinal chemist's arsenal to strike a fine balance in multiparameter optimization campaigns and to deliver the best molecules for further preclinical development. The piperidine heterocycle, a dominant fragment in drug discovery, is often targeted for such replacement in attempts to improve potency and ADME (absorption, distribution, metabolism, excretion) profile. In this manuscript we explore 4H-Dewar pyridines (4H-DP) as rigid programmable isosteres of equatorially and elusive axially substituted piperidines. These fragments are readily accessible via pyridine dearomatization without the need for expensive catalysts and reagents. A wide spectrum of available reactivities enables incorporation of 4H-DP in various structural contexts. Exit vector analysis (EVA) underscores topological similarity with the parent piperidine as well as complementarity with the previously reported bioisosteres.*

4-Substituted piperidines belong to a group of privileged fragments in drug discovery.[1] This substructure is commonly found in drug leads across major therapeutic areas and modalities beyond small molecules (Figure 1a).[2–5] In these instances, piperidine is deployed either as a primary pharmacophore responsible for target binding or as a linker with predictable exit vectors and favorable physiochemical properties. However, the piperidine substructure often bears liabilities that prevent candidate progression in preclinical development (*vide infra*). To address these challenges and to fine-tune the desired properties, medicinal chemists often rely on bioisosteric replacement tactics.[6] Genesis of new rigid sp^3-rich bioisosteres is a flourishing field with bicyclopentane (BCP) representing its current paragon[7–12]. Curiously, despite major prevalence of piperidine in drug design[13] the space of its analogues has

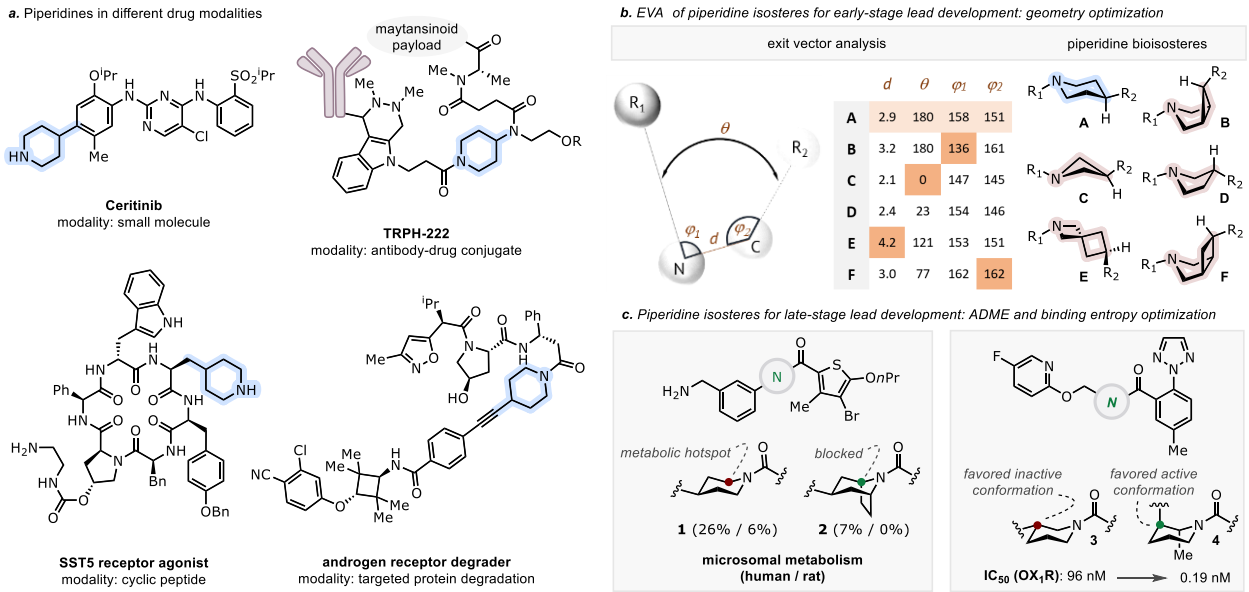
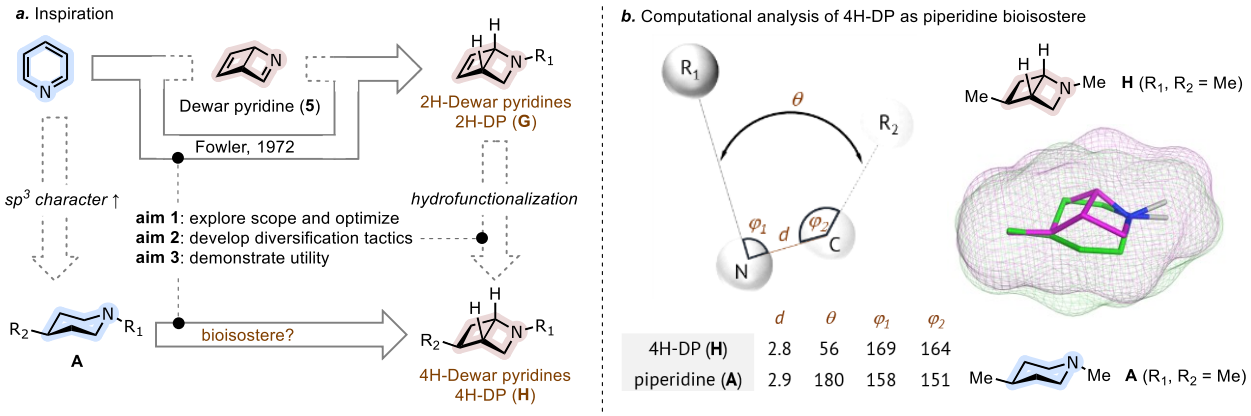


Figure 1. a) Different modalities of piperidine-containing drugs and drug candidates. b) Exit vector analysis (EVA) of 4-substituted piperidine (**A**) and selected "state-of-the-art bioisosteres" (**B, C, D, E, F**). c) Documented examples of improvements in metabolic profile or potency by rigidifying the piperidine linker.

experienced a more placid growth compared to BCPs as benzene surrogates. Established piperidine (**A**) bioisosteres (**B, C, D, E, F**) are commonly used in early lead development with the purpose of altering the spatial orientation and distances between vectors and to optimize the binding affinity, as evident from the exit vector analysis (EVA, Scheme 1b).[14]

A different stratagem is necessary for later stages of lead advancement, however. That is to optimize the ADME (absorption, distribution, metabolism, excretion) profile without significantly perturbing the molecular topology. One of the major liabilities of the piperidine substructure is the presence of metabolic hotspots, where CYP-catalyzed oxidation leads to ring-opening and formation of reactive electrophiles.[15] Increased resistance towards hepatic metabolism is observed in some cases where alkyl substituents are introduced to impede the deleterious oxidation. For example, piperidine-tropane replacement within the β-tryptase inhibitor (**1**→**2**) significantly improved stability in rat and human microsomes (Figure 1c, left inset).[16] On the other hand, this positive impact can be offset by the increase in molecular weight, total surface area, and overall lipophilicity, features commonly associated with off-target toxicity.[17] Piperidines are also conformationally flexible. This flexibility effectively dilutes the concentration of the bioactive conformation and imposes entropic penalties due to the conformational sampling within the targeted enzyme.[18,19] Therefore, a more rigid core with fewer available conformations can offer a significant boost in potency. Perhaps the best illustration of this paradigm is the case of orexin receptor antagonist **3**, where the incorporation of a single methyl group (**4**) changes the conformational landscape and leads to a 505-fold increase in potency (Figure 1c, right inset).[20] Stark examples like this are often rationalized as a manifestation of the "magic methyl effect" and have galvanized the development of numerous C–H methylation methodologies.[21–25] Importantly, however, a single methyl group might not be sufficient to bias conformational preference in all contexts. Therefore, the advent of rigid congruent piperidine bioisosteres could provide new opportunities in drug discovery and become a valuable tool in medicinal chemist's arsenal.

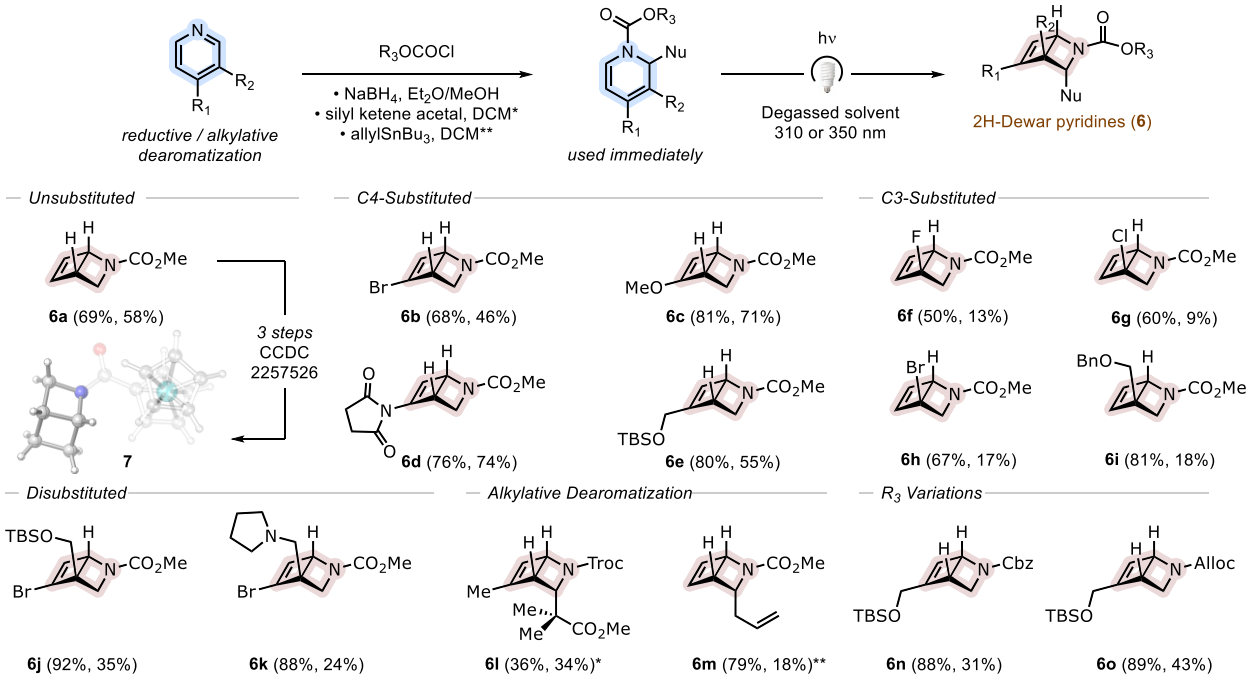
In 1972, Fowler described a method for reductive dearomatization of pyridine followed by photochemical 4π-electrocyclization (Scheme 1a).[26] This seminal work remained largely overlooked with only a few follow-up studies.[27,28] The corresponding products were mostly leveraged as intermediates for accessing polymers[29] or other rearranged scaffolds.[30–38] In contrast, we were intrigued by these [2.2.0]-bicyclic products in their own right. The compact, sp^3-rich nature of *N*-heterocyclic compounds **H** inspired us to evaluate them as piperidine isosteres, to showcase their utility, and to develop a toolkit for their incorporation into drug molecules. If successful, this design would have several benefits: 1) substituted pyridines are commodity chemicals and are thus readily available; 2) spring-loaded nature of the olefin in **G** can facilitate its functionalization and structural diversification; 3) the synthesis of **H** is atom- and step-economical, fulfilling the imperative conditions for its widespread dissemination. We reimagined the overall transformation as a formal reductive difunctionalization of fleeting Dewar pyridine **5** – and hence propose the term "tetrahydro-Dewar pyridine (4H-DP)" for the **H** substructure (Scheme 1a).



Scheme 1. a) Inspiration for more rigid piperidine isosteres with the same number of carbon atoms. b) EVA (exit vector analysis) comparison between piperidine (**A**) and 4H-Dewar pyridine (**H**). Overlap between **A** and **H** (R_1 = R_2 = Me).

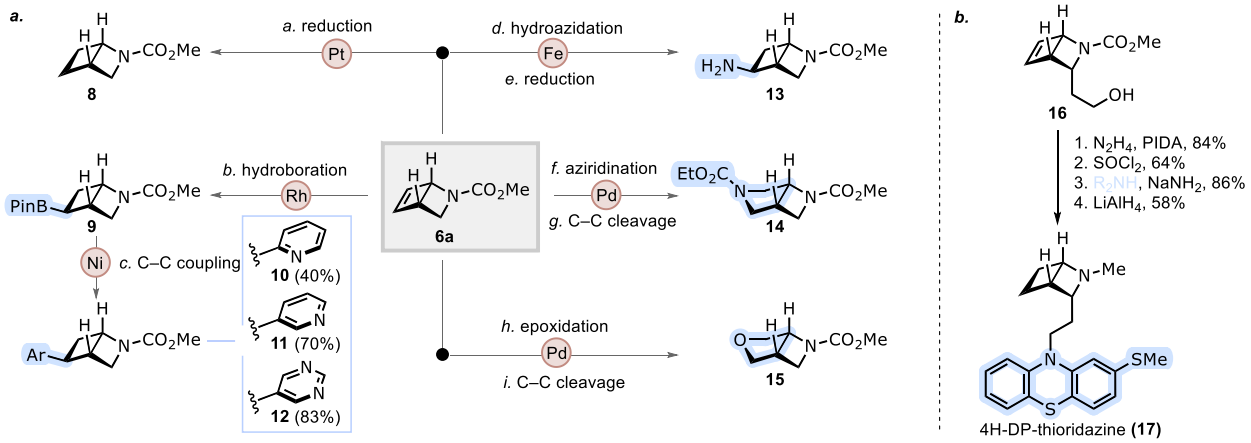
First, we evaluated our hypothesis of 4H-Dewar pyridine acting as piperidine isostere through computational analysis of the respective geometries (Scheme 1b). Conformational search followed by energy minimization delivered an optimized conformation of 4H-Dewar pyridine **H**. To our delight, interatomic distance across the ring system and directionality of exit vectors matches well with that of the parent piperidine **A**. Moreover, both fragments occupy nearly identical volume, validating the envisioned design.

With these encouraging results, we proceeded to explore the substitution pattern of dihydro-Dewar pyridines (2H-DP) **6**, accessible through the dearomatization/electrocyclization strategy (Scheme 2). After an optimization campaign (see SI for details), the pyridine scope was evaluated. Parent pyridine underwent dearomatization using methyl chloroformate as an electrophile followed by light-mediated 4π-electrocyclization in 69% and 58% yield, respectively, affording 2H-DP **6a**. Atom connectivity was confirmed with single crystal X-ray diffraction analysis of the ferrocenecarboxylic acid derivative **7** (after olefin hydrogenation). Notably, experimental geometrical parameters were in line with *in silico* generated data. In general, C4-substituited pyridines were the most efficient substrates for the dearomatization/electrocyclization sequence. Thus, bromo (**6b**), methoxy (**6c**), succinimide (**6d**), and protected hydroxymethylene (**6e**) containing 2H-Dewar pyridine analogues were obtained in good yields. The broad spectrum of tolerated functionalities facilitates downstream derivatizations (*vide infra*). Empowered by the regioselective dearomatization of C3-substituted pyridines[39], we were able to incorporate substituents at the bridgehead position of the bicyclic products. In this fashion, 2H-Dewar pyridines bearing fluorine (**6f**), chlorine (**6g**), and bromine (**6h**), as well as protected hydroxymethylene group (**6i**), a precursor to an unorthodox β-amino acid, at the C3 position were synthesized. Even though the reaction yields were low in certain cases, we argue that the reagent cost, the unchallenged IP-space, and the utility of the products offset this shortcoming. Next, we demonstrated that the C2 functionalization is feasible by virtue of alkylative rather than reductive dearomatization. In this fashion **6l** and **6m** were obtained using a silyl ketene acetal derivative and allyltributylstannane as nucleophiles, respectively. Disubstituted pyridines were also competent substrates in this reaction sequence affording products (**6j**, **6k**) equipped with three exit vectors. Finally, we demonstrated that Cbz or Alloc activating groups were tolerated, allowing for flexibility in the protecting group selection (**6n**, **6o**).



Scheme 2. Substrate scope. Reactions were routinely performed on 1 to 40 mmol scales using a slight excess (1.1 to 1.3 eq) of reagents. See SI for more information.

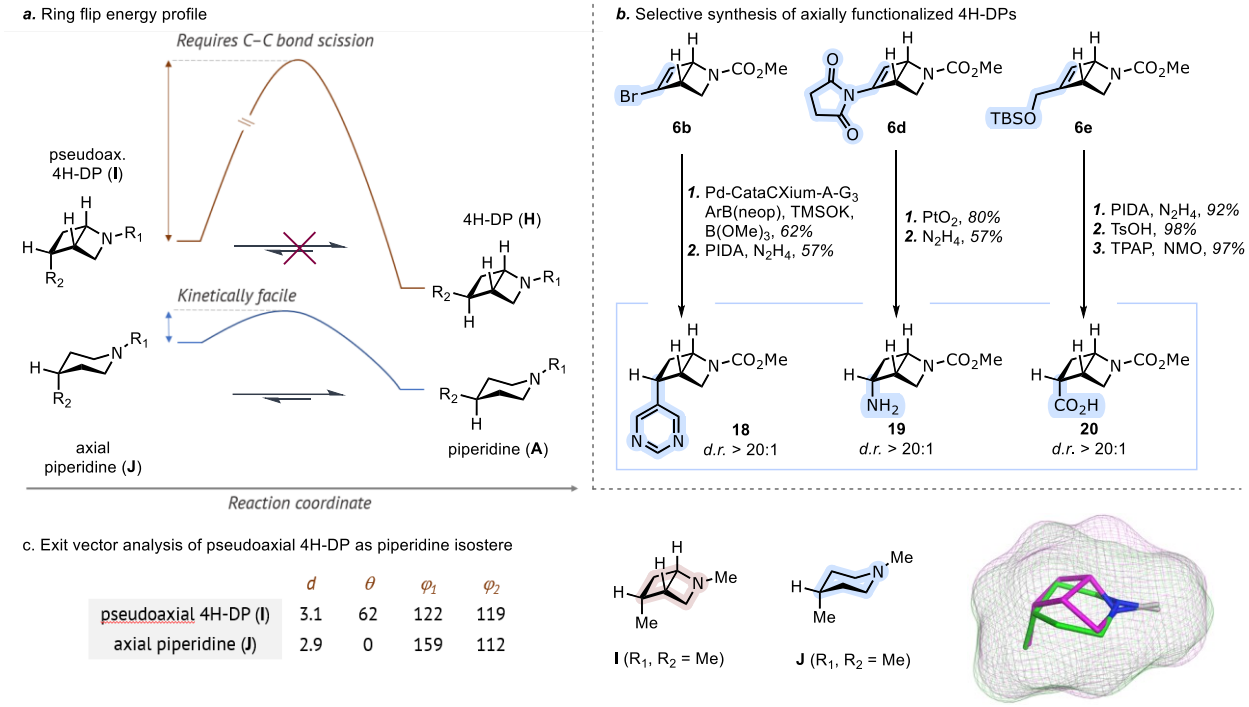
Having examined the scope of pyridines for the dearomatization/electrocyclization sequence, we progressed towards our next aim: the development of diversification tactics for a seamless incorporation of 4H-Dewar pyridines into drug-like molecules using **6a** as a platform. From the outset we anticipated high reactivity of the strained bridging C–C bond. Indeed, classical hydrogenation conditions using palladium on carbon resulted in its cleavage. However, milder Adams' catalyst afforded 4H-Dewar pyridine **8** in 78% yield. Rhodium-catalyzed hydroboration was employed to access pinacol boronic ester **9**. Due to the lack of inherent substrate bias, the ligand is capable of exerting modest control over regioselectivity delivering the desired isomer in 1.7:1 selectivity (see SI for a full ligand screen). To showcase downstream reactivity of this versatile intermediate, boronic ester **9** was engaged in dual photoredox/nickel catalyzed sp^2-sp^3 cross-coupling[40] with heterocyclic aryl bromides. Thus, 2-pyridyl (**10**), 3-pyridyl (**11**), and 5-pyrimidyl (**12**) analogues were obtained in good yields. Alternatively, the desired C–C bond can be forged via reductive Heck coupling directly from **6a** in excellent yields (see SI for details). Iron mediated radical hydroazidation[41] of **6a** followed by Staudinger reduction furnished 4H-DP **13**, an isostere of the renowned 4-aminopiperidines. Notably all of the aforementioned hydrofunctionalizations proceeded in excellent diastereoselectivity due to the puckered shape of 2H-Dewar pyridines. Furthermore, olefin aziridination and subsequent C–C bond hydrogenolysis yielded [5,4]-bicycle **14**, shortening the known route[42] to this building block. Analogously, tetrahydrofuran-containing congener and morpholine isostere **15** was obtained via similar epoxidation/hydrogenolysis sequence. To further illustrate the ease of incorporation of 4H-Dewar pyridines into drug molecules we synthesized 4H-Dewar pyridine analogue of thioridazine (Scheme 3). 2H-DP **16** was reduced by the *in situ* generated diimide followed by a two-step alcohol amination and carbamate reduction delivering **17** in 34% yield over 4 steps.



Scheme 3. Left: Formal "hydrofunctionalizations" of **6a** and skeletal editing of the Dewar pyridine scaffold (major isomer depicted). Right: Synthesis of 4H-Dewar pyridine thioridazine isostere (**17**). a) 9 mol% PtO_2, 1 atm H_2, MeOH, 22 °C, 1 h, 78%, b) 1.25 mol% $(Rh(COD)Cl)_2$, 2.5 mol% xantphos, 1.2 eq. HBPin, THF, 22 °C, 16 h, 92%, *r.r.* = 1.7:1, c) 1.5 eq. morpholine, 5 mol% $Ni(DME)Cl_2$, 1 mol% $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$, 5 mol% dtbbpy, DMF, blue LEDs, 22 °C, 2 h, see SI for *r.r.,* d) 2 eq. $Fe_2(ox)_3 \cdot 6H_2O$, 6.4 eq. $NaBH_4$, 3 eq. NaN_3, 0 °C, 35 min, 52%, *r.r.* = 2.0:1, e) 18 mol% PtO_2, 1 atm H_2, MeOH, 22 °C, 16 h, quant. f) 3 eq. EtOOCNHONs, 21 mol% $BnEt_3NCl$, 6 eq. $NaHCO_3$, DCM/H_2O, 0 °C to 22 °C, 4 h, 44% over 2 cycles, g) 10 mol% Pd/C, 1 atm H_2, MeOH, 22 °C, 16 h, 72%, h) 3 eq. *m*-CPBA, 6 eq. $NaHCO_3$, 0 °C to 22 °C, 16 h, 67%, i) 10 mol% Pd/C, 1 atm H_2, MeOH, 22 °C, 2 h, 73%.

As alluded to above, conformational flexibility of piperidine can decrease the potency due to the dilution of bioactive conformation. 4H-Dewar pyridine analogues can address this drawback as their transverse C–C bond substantially increases the energy barrier for a ring-flip (Scheme 4a). Therefore, this isostere provides an opportunity to selectively access pseudo-axial piperidine isosteres without introducing auxiliary groups, which could disturb interactions with their targets. This technique can become especially valuable for hypothesis testing during lead optimization by bypassing laborious X-ray analysis. Thus, we set out to exemplify this aspect of 4H-Dewar pyridine design through the synthesis of several functionalized pseudo-axial isosteres (Scheme 4b). Towards this goal, vinyl bromide **6b** was subjected to palladium-catalyzed anhydrous Suzuki coupling[43] followed by a diimide reduction delivering the arylated product **18**, the epimer of **12**. Catalytic hydrogenation and deprotection of enamine **6d** afforded the pseudo-axial diamine **19**, the epimer of **13**. Finally, **6e** was subjected to a three-step redox and protecting group

manipulation sequence furnishing the amino acid **20** in 87% overall yield. As expected, profound substrate bias afforded exquisite stereoselectivity in all cases. In line with the pseudo-equatorial case, our computational analysis displayed a close match of geometrical parameters and overall volume between the axial conformation of the parent 1,4-dimethylpiperidine (**I**) and its 4H-Dewar pyridine counterpart (**J**) (Scheme 4c).



	d	*θ*	φ_1	φ_2
pseudoaxial 4H-DP (**I**)	3.1	62	122	119
axial piperidine (**J**)	2.9	0	159	112

Scheme 4. a) Energy profiles for "ring flip" in 4-substituted piperidine and its 4H-Dewar pyridine isostere. b) Synthesis of 4H-Dewar pyridine isosteres with functional handles in pseudoaxial position. c) EVA comparison of pseudoaxial 4H-Dewar pyridine isosteres and overlap between **I** and **J** ($R_1 = R_2 = Me$).

In this study, we introduced 4H-Dewar pyridines as innovative isosteres of piperidines supported by geometry optimization and exit vector analysis. Broad substrate scope, a diverse array of downstream derivatization, and functionalization of five out of six core sites was demonstrated, which will hopefully bolster its wide adaptation among practitioners. The bicyclic design brings several notable advantages such as precise control over spatial orientation of exit vectors and rigidification of the core without increase in molecular weight. Finally, 2H-Dewar pyridines are accessible in only two steps from feedstock pyridines without the need for expensive reagents or catalysts. The prevalence of the piperidine substructure in drug discovery extends far beyond the small molecule realm. Thus, we believe that the outlined work will equip explorers with a convenient tool for making subtle yet impactful structural modifications.

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