The Fluoro-Pauson—Khand Reaction in the Synthesis of Enantioenriched Nitrogenated Bicycles Bearing a Quaternary C—F Stereogenic Center

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

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Supporting Information

Organic Letters

ABSTRACT: A variety of enantioenriched fluorinated 6H-cyclopenta-[c]pyridin-6-one bicycles, a scaffold present in several classes of monoterpenic alkaloids with varied biological activity, were synthesized in just five steps from simple aldehyde starting materials. The synthesis presented wide functional group tolerance and moderate to high yields and diastereoselectivities and could be carried out on a gram scale. These products were suitable for further transformations, such as hydrogenation and deprotection of the *tert*-butylsulfonyl protecting group.

N itrogen-containing heterocycles are highly prevalent in pharmaceuticals and agrochemicals as well as in other bioactive molecules. This is immediately apparent upon consideration of the alkaloid class of natural products; morphine, caffeine, nicotine, and atropine all belong to this diverse family and present a wide range of biological activities. A somewhat understudied scaffold is the cyclopenta[c]pyridin-6one bicycle, present in various natural products such as tecomanine, tecostanine, and certain compounds belonging to the kinabalurine series (Figure 1).^{1,2} Both tecomanine and tecostanine are present in the leaves of *Tecoma stans*, a species of



Figure 1. Structures of monoterpenic alkaloids bearing the target bicyclic structure.

Fluorinated monoterpenic alkaloid analogues Stereoselective construction of quaternary C-F bond Use of vinyl fluorides in the Pauson-Khand reaction

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bush native to Latin America, infusions of which have long been used in Mexico to treat symptoms of diabetes. In fact, extracts of this plant have been shown to exert a significant hypoglycemic response in both rabbits and dogs, attributed to the action of these two monoterpenic alkaloids.^{3,4} In view of this activity, compounds presenting this bicyclic structure could be useful in the search for new antidiabetic compounds, a class of pharmaceuticals that is increasingly important in the modern world.⁵

In terms of synthesis, racemic tecomanine has been synthesized through a variety of synthetic methods, including a Pauson–Khand reaction, which allows the prior introduction of all of the necessary substituents directly into the precursor and creates the bicyclic molecular complexity in just one reaction (Scheme 1a).⁶ Series of enantioenriched products with similar structures have been prepared by both Gais⁷ and Evans,¹ again through the use of a Pauson–Khand reaction as the key step to form the bicyclic scaffold.

On the other hand, fluorine has become increasingly important in several key industrial fields, including but not limited to medicinal and pharmaceutical chemistry, agrochemistry, and materials science. The strategic incorporation of fluorine into biologically active molecules can improve the drug-like properties of a given compound, such as the metabolic

Received: July 22, 2019

Scheme 1. (a, b) Previous Related Work on the Racemic Synthesis of Tecomanine Precursor and Other Trifluoromethylated Derivatives via the Pauson-Khand Reaction; (c) Synthesis of Enantioenriched Fluorinated Tecomanine Analogues Reported in This Work

a) Racemic synthesis of Tecomanine precursor⁶



stability or lipophilicity.^{8–10} However, because of the scarcity of natural products containing fluorine atoms, any advance in this field relies on the development of new methods to synthesize new fluorine-bearing structures. A recent trend in medicinal organic chemistry, denominated the escape from flatland, refers to a shift from the more common aromatic and similar C_{sn}^2 tethers toward C_{sp}^{3} centers in an attempt to provide greater 3D molecular diversity.¹¹ In particular, after approximately a decade of exhaustive research on the formation of C_{sp}^2 -F and C_{sp}^2 -R_F bonds,¹² the asymmetric introduction of fluorine or fluorinated groups at sp³ carbon centers has gained more attention in recent years.¹³ With regard to this objective, perhaps the most challenging step is the selective construction of a quaternary stereogenic carbon center containing a C-F bond. In fact, pharmaceutical drugs containing a stereogenic C-F bond constitute just 1% of the drugs currently on the market as a direct result of this problem.

We recently reported the first Pauson–Khand reactions using enyne substrates containing a vinyl fluoride moiety as the olefin coupling partner, which proved to be an effective way to construct molecular complexity and the coveted quaternary C– F group in one step, albeit in a racemic manner.¹⁴ Because of the complete diastereoselectivity observed in this process, we foresaw that enantiopure products bearing a stereodefined quaternary C–F unit within a similar monoterpenic skeleton could be obtained by using a suitable enantioenriched substrate.

We were surprised to find that fluorinated examples of this class of structure had not yet been studied, the only example in the literature being a single racemic analogue based on the same 6H-cyclopenta[c]pyridin-6-one scaffold bearing a trifluoromethyl substituent, which was also synthesized using the Pauson–Khand reaction (Scheme 1b).¹⁵

Therefore, we decided to apply our method to the synthesis of enantioenriched compounds presenting the same bicyclic skeleton as seen in the aforementioned natural products, bearing an all-important C-F bond at the bridged stereogenic center (Scheme 1c).

We first carried out a retrosynthetic analysis of our target structures (Scheme 2). The bicyclic core could be constructed

Scheme 2. Retrosynthetic Analysis of Target Bicyclic Structures



via a fluoro-Pauson-Khand reaction of the *N*-tethered fluoroenyne precursor. The vinyl fluoride could be introduced using a suitable building block for the alkylation of the amine group, which could in turn be synthesized through stereo-selective propargylation of the corresponding imine.

We then decided that Ellman's *tert*-butanesulfinyl imines would be suitable starting materials for our goal of synthesizing tecomanine analogues since they can be used as electrophiles in many diastereoselective addition reactions with a variety of nucleophiles such as organometallic reagents.^{16,17} Specifically, the diastereoselective addition of propargylmagnesium bromide to this class of imines is well-documented. Therefore, we followed the procedure reported by Zhang et al. to obtain a variety of sulfinylamide intermediates **2** in good yields with high diastereoselectivities.¹⁸ Aromatic, heteroaromatic, and aliphatic aldimines participated in the propargylation step uneventfully.

From there, the final step to form the precursors for the Pauson–Khand reaction was the introduction of the fluoroallyl group via alkylation of the nitrogen atom. Unfortunately, the direct alkylation of the sulfinylamides resulted in unsatisfactory yields (<20%). However, we found that after oxidation to the corresponding sulfonamides, the reaction took place much more successfully.¹⁹ In this way, a series of *N*-tethered fluorinated enynes **4** were synthesized in good to high yields (Scheme 3).

We then applied our fluoro-Pauson-Khand procedure to the desired precursors 4 (Scheme 4).¹⁴ However, our previously reported conditions using dichloromethane at 40 °C for the second reaction step were unsuccessful for these substrates. Instead, we found that we had to switch the solvent to dichloroethane and increase the temperature slightly to 65 °C. The final bicyclic products were obtained in moderate to good yields with excellent diastereoselectivities (dr >20:1). The reaction was tolerant of a variety of electron-neutral and electron-rich aromatic rings with several substitution patterns (6a-e). The presence of a halogen atom on the aromatic ring was also tolerated (6f). Heteroaromatic substituents at the stereogenic center resulted in interesting scaffolds combining two potential pharmacophores (6g-j). However, pyridinebased 6j resulted in a low yield (see the Supporting Information for details).²¹ Substrates derived from aliphatic aldehydes, both linear and cyclic, were also successfully used (6k-n). The absolute stereochemistry of product 6a was determined to be



^{*a*}The reaction was carried out as described by Zhang et al.¹⁸ Standard conditions for the propargylation step: aldimine **1** (1 equiv), freshly prepared propargylmagnesium bromide (1.5 equiv), dichloromethane (0.1 M), -48 °C, 16 h. ^{*b*}Standard conditions for the oxidation step: **2** (1 equiv), *m*-CPBA (1.2 equiv), dichloromethane (0.1 M), 0 °C to r.t., 2 h. ^{*c*}Standard conditions for the fluoroallylation step: **3** (1 equiv), NaH (3 equiv), **5** (2 equiv), DMF (0.2 M), 0 °C to r.t., 16 h. ^{*d*}Mesylate **5** was prepared following the procedure described by Mykhailiuk et al.²⁰ ^{*e*}An extra reduction step was necessary for the synthesis of **4j** (see the Supporting Information for details). ^{*f*}Isolated yields of the final fluoroallylation step are shown.

(*S*,*R*) by X-ray crystallography (see the Supporting Information for details) (Scheme 4).

The double bond in the resulting bicyclic products **6** could be efficiently and diastereoselectively (dr >20:1) hydrogenated using palladium over activated charcoal under an atmosphere of hydrogen.²² However, it is worth noting that the resulting saturated product 7 was unstable under acidic conditions and rapidly lost HF during column chromatography using both standard silica gel and aluminum oxide (Scheme 5a).

Nonetheless, using FluoroFlash silica gel we were able to purify the desired saturated cyclopentanones 7 successfully with no loss of HF. Furthermore, the *tert*-butylsulfonyl group could be removed through treatment of the resulting Pauson–Khand adduct with trifluoromethylsulfonic acid in the presence of anisole to form 8 (Scheme 5a).²³ The resulting amine was isolated as the hydrochloride salt, as the intermediate free amine was found to be unstable. A gram-scale synthesis of **6a** was carried out successfully in good yield with no detectable decrease diastereoselectivity (Scheme 5b).

In summary, the power of the intramolecular Pauson–Khand reaction for the stereoselective construction of enantioenriched bicyclic cyclopentenones has been showcased by the concise asymmetric synthesis of fluorinated tecomanine analogues. Noteworthy is the use of vinyl fluorides as olefin counterparts in the Pauson–Khand reaction, allowing the stereoselective introduction of a fluorine atom in an otherwise synthetically challenging bridgehead quaternary stereocenter. Several synthetic transformations have been carried out on the obtained products, including hydrogenation of the unsaturated bicyclic system to generate the corresponding saturated derivative and

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Scheme 4. Scope and Limitations of the Fluoro-Pauson-







the removal of the Bus protecting group. A gram-scale synthesis has also been successfully achieved in five steps starting from the corresponding aldehyde.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02557.

Experimental procedures, characterization of all new compounds, and their corresponding NMR spectra (PDF)

Accession Codes

CCDC 1937096 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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The manuscript was written through contributions of all authors. All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to the Spanish MICINN and the AEI (CTQ2017-84249-P) for financial support, the SCSIE (Universitat de València) for access to instrumental facilities, and M. R. Pedrosa (Universidad de Burgos) for providing us with MoO_2Cl_2 . The technical and human support provided by SGIker (UPV/EHU, MINECO, GV/DJ, ERDF, and ESF) is also gratefully acknowledged. P.B. thanks the Spanish Ministry of Economy for a Ramón y Cajal contract (RyC-2016-20951). The authors are also grateful to Jose Cabeza for assistance in the synthesis of certain starting materials.

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