Organic LETTERS

Letter

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Asymmetric Synthesis of Monofluorinated 1-Amino-1,2-dihydronaphthalene and 1,3-Amino Alcohol Derivatives

Rubén Lázaro,[†,‡] Raquel Román,[†] Daniel M. Sedgwick,[†] Günter Haufe,[§] Pablo Barrio,*[,†] and Santos Fustero*[,†,‡]

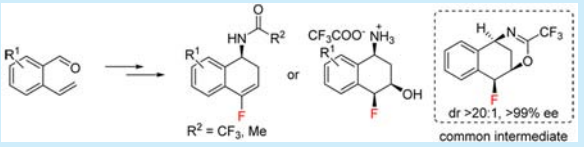
[†]Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain

[‡]Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain

[§]Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstrasse 40, D-48149 Münster, Germany

Supporting Information

ABSTRACT: Enantioenriched 1-amino-4-fluoro-1,2-dihydronaphthalene derivatives are accessed via two complementary synthetic strategies. The careful optimization of the reaction conditions required for the elimination step in one route has allowed both the identification of an anchimerically assisted reaction pathway and, more importantly, access to a divergent reaction pathway toward fluorinated 1,3-amino alcohols from a common intermediate just by adjusting the number of equivalents of base used.



The increasing importance of organofluorine chemistry is unquestionable.[1] The impact that organofluorine compounds have had in key industrial fields such as the pharmaceutical,[2] agrochemical,[3] or materials industries[4] makes it hard to conceive our everyday life without them. The vast developments in the synthesis of monofluorinated organic compounds during the past decade have recently been covered by Paquin.[5] Specifically, fluorolefins display an array of features that have made them valuable building blocks in organic synthesis[6] found in antidiabetes and anti-HIV drugs, among others (Figure 1).[7] Perhaps the most characteristic feature of

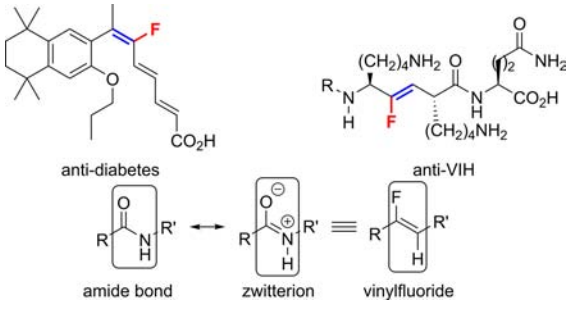


Figure 1. Fluorolefin-containing drugs and bioisosterism with amides.

fluorolefins is their bioisoterism with an amide group (Figure 1).[7c,8] The stereoelectronic resemblance between these two subunits allows the introduction of fluorolefins in peptidomimetics, mimicking an amide bond without suffering from proteolytic degradation.[9]

In our continuing effort to expand the use of 2-halobenzaldehyde derivatives in the context of diversity-oriented synthesis (DOS),[10−12] we envisioned the asymmetric synthesis of fluorine containing 1-amino-1,2-dihydronaphthelene derivatives as a new synthetic challenge (Figure 2). Specifically, we aimed to use a

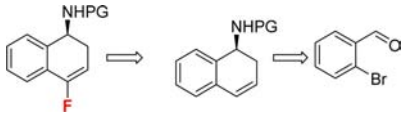
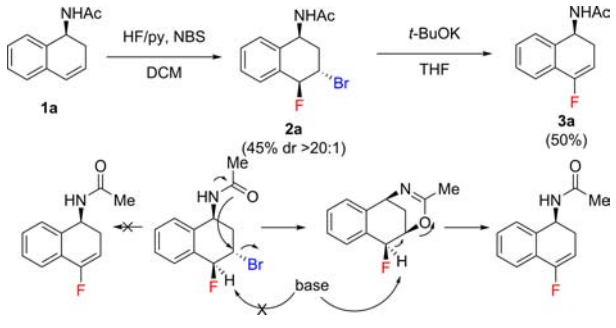


Figure 2. Proposed retrosynthesis for 1-amino-1,2-dihydronaphthalene-derived vinyl fluorides.

common precursor from our recently reported one-pot allylation/RCM procedure, which has already been transformed into the corresponding bromolefin en route toward the synthesis of sertraline.[10e] Herein, we describe the transformation of such intermediates into the corresponding new benzo-fused vinylfluoride analogues[13] along with some insight into the mechanism of the elimination step leading to it (Figure 2).

We began our study by subjecting *N*-acetylated substrate **1a** to the reaction conditions originally developed by Olah for the bromofluorination of olefins, affording **2a** in moderate yield and complete diastereoselectivity (Scheme 1).[14,15] The relative

Scheme 1. Preliminary Experiment

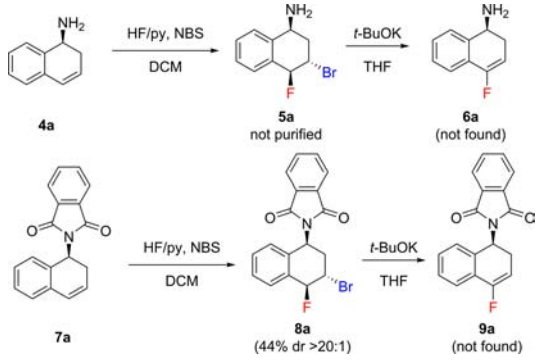


Received: December 26, 2015
Published: February 17, 2016

DOI: 10.1021/acs.orglett.5b03671
Org. Lett. 2016, 18, 948−951

configuration of the two new stereocenters was ascertained by means of 2D-NMR NOESY experiments (see the Supporting Information). The exchange of the protecting group was essential given that the *tert*-butylsulfinyl group proved incompatible with the reaction conditions (HF·Py). *t*-BuOK-mediated elimination proceeded uneventfully, affording the desired vinyl fluoride **3a** in moderate yield (Scheme 1).[16] The formation of the latter made us question if the elimination of HBr, required to obtain the target molecule, might proceed with the participation of the neighboring amine protecting group,[17] since direct E2 elimination is precluded due to the lack of a proton in the benzylic position *anti* to the bromine atom (see Scheme 2).[18]

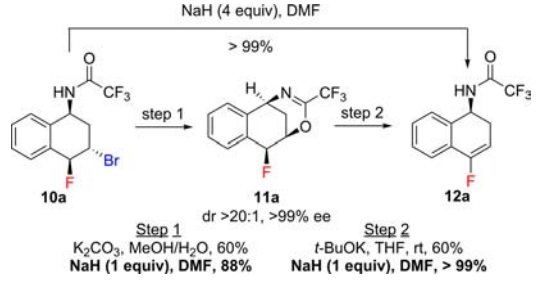
Scheme 2. Evidence for an Anchimeric Assistance Pathway



Should this be correct, the reaction would only take place with amine protecting groups able to undergo similar processes. In order to find some preliminary support for our hypothesis, we carried out the reaction sequence on the unprotected derivative **4a** (Scheme 2). In addition, the corresponding phthalimide derivative was also tested, since imides are known not to participate as neighboring groups in processes of this kind (Scheme 2). The corresponding bromofluoro compounds were then synthesized in moderate yield and subjected to elimination conditions using *t*-BuOK as the base (Scheme 2).[19] In agreement with our hypothesis, the formation of vinyl fluorides **6a** or **9a** was not observed (Scheme 2).

Related anchimeric assistance processes have been reported in the literature by several authors with the corresponding dibromo derivatives.[20] Inspired by these reports, we selected the trifluoroacetyl protecting group due to its enhanced participation in neighboring group processes along with its ease of removal by treatment with K_2CO_3 in MeOH/H_2O. The corresponding trifluoroacetylated substrate **10a** was then synthesized, and the reaction conditions for the elimination step were subsequently optimized (Scheme 3). First, we found that the reaction

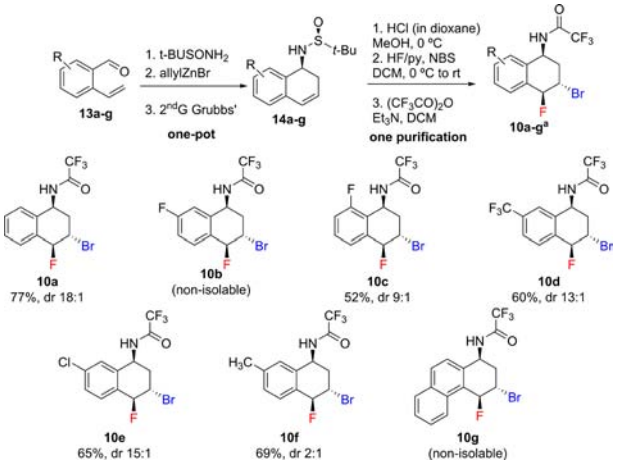
Scheme 3. Optimization of the Reaction Conditions for Substrate 7a



conditions reported by Vasella (K_2CO_3, MeOH/H_2O)[20b] afforded the tricyclic structure **11a** in a moderate 60% yield which could be improved to 88% through the use of NaH in DMF (Scheme 3).[20a] This intermediate was then subjected to further elimination, with NaH in DMF once again being the optimal condition (Scheme 3). In view of the observed results, we considered carrying out both elimination steps in a tandem fashion by using excess NaH in DMF, affording fluoroolefin **12a** in a quantitative yield (Scheme 3). Although the synthesis of **12a** was our initial objective, the ability to isolate **11a** in excellent yield permitted the diversification of molecular architectures obtainable by our methodology (vide infra).

With these optimized reaction conditions in hand, we studied the scope and limitations of this transformation using bromo- and fluorotrifluoroacetamides **10a−g**. These compounds were synthesized from various substrates **14a−g** affordable by our previously described one-pot methodology[10e] following a three-step procedure with only one chromatographic purification (Scheme 4). Most compounds were obtained in good to excellent

Scheme 4. Optimized Synthesis of Substrates 10a−h



[a]Yields for the second three-step, one-purification reaction sequence.

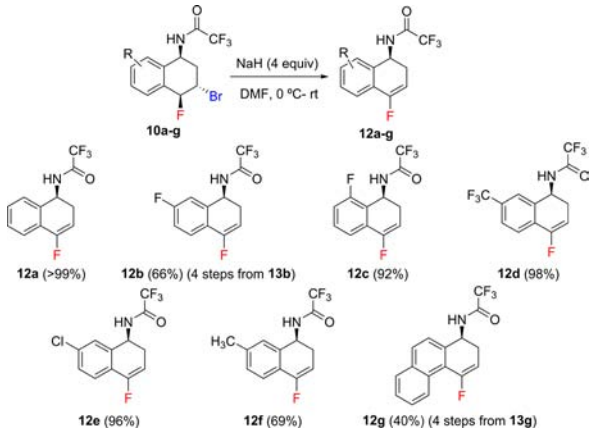
overall yields for a three-step procedure (**10a**,**c−e**); however, the introduction of a moderately electron-donating methyl group at position 6 in **10f** resulted in a significantly lower yield along with a diminished diastereoselectivity (Scheme 4). Nevertheless, for all of the other examples the diastereoselectivities ranged from good to excellent. Compounds **10b** and **10g** could not be isolated, so the crude material from this three-step reaction sequence was used in a fourth step (vide infra).

Having prepared an array of bromofluoro derivatives **10**, we subjected them to the optimized reaction conditions shown in Scheme 3 for the synthesis of the corresponding fluoroolefins **12**. The reactions proceeded in good to excellent yields (69 → 99%) with electron-neutral (**10a**), electron-deficient (**10b−e**), or moderately electron-rich substrates (**10f**). Interestingly, compounds **12b** and **12g** were obtained in good yields via a four-step sequence with a sole chromatographic purification from **13b**,**g** due to the instability of the corresponding bromofluoro intermediates **10b**,**g** (Scheme 5).

As mentioned previously, the isolation of **11a** in an excellent >99% yield and complete diastereo- and enantiopurity encouraged us to explore one further reaction pathway. TFA-mediated hydrolysis of cyclic trifluoroimidates of this kind provides a straightforward access to *cis*-1,3-amino alcohols.[22]

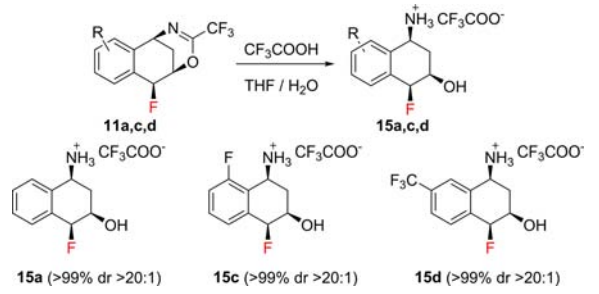
DOI: 10.1021/acs.orglett.5b03671
Org. Lett. 2016, 18, 948−951

Scheme 5. Scope and Limitations[21]



However, to the best of our knowledge, this transformation has never been applied to the synthesis of fluorine-containing 1,3-amino alcohols. Thus, various representative tricyclic oxazocines **11a,c,d** were synthesized by using 1 equiv of NaH (see Scheme 3)[19] and treated with TFA in wet THF affording *all-cis* fluorinated 1,3-amino alcohols **14a,c,d** in quantitative yields and with complete control over both the relative and the absolute stereochemistry (Scheme 6).

Scheme 6. Synthesis of Stereodefined Fluorinated 1,3-Amino Alcohols



Finally, we set out to reduce the number of steps necessary to afford benzo-fused fluoroolefin derivatives like **12** or **3**. Based on our own experience, we envisioned that *o*-(1-fluorovinyl)-benzaldehyde derivatives (OFVBA) could serve as starting materials for our condensation/asymmetric allylation/RCM sequence (Figure 3).

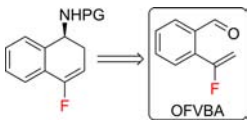
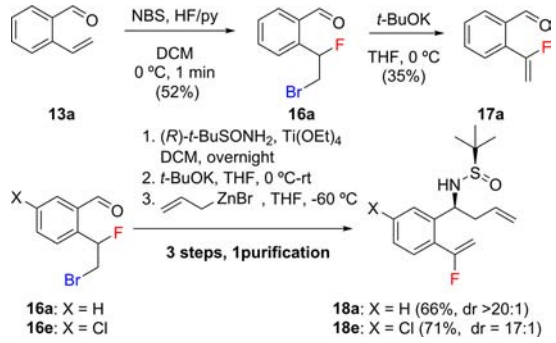


Figure 3. Alternative retrosynthetic approach.

Astonishingly, we found that 2-(1-fluorovinyl)benzaldehyde derivatives were not known compounds, so our first challenge was to set up a suitable synthetic route toward such promising fluorinated building blocks. First, 2-vinylbenzaldehyde was treated with HF·Py/NBS affording the corresponding 1,2-bromofluoro compound **16a** in just 1 min in a moderate 52% yield (Scheme 7). *t*-BuOK-mediated elimination afforded the desired OFVBA **17a** in a poor 35% yield (Scheme 7), which proved to be instable and volatile making its handling somewhat

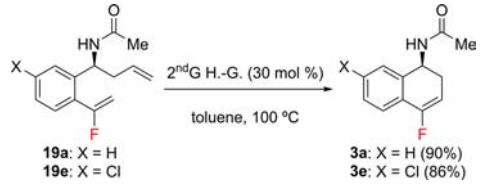
Scheme 7. New Strategy, Initial Steps



inconvenient. In light of this unanticipated and undesired outcome, we decided to carry out the condensation with the chiral auxiliary on bromofluoro intermediates **16a,b** followed by elimination and asymmetric allylation using a three-step/one-purification procedure in synthetically acceptable yields and excellent diastereoselectivities (Scheme 7).

After failing at accomplishing the final RCM on substrate **18a**,[23] we were pleased to find that by simply exchanging the protective group at the nitrogen to acetyl (78−99% yield) the desired transformation could be afforded in 90% yield (Scheme 8).[19] This reaction sequence was also applied to the synthesis of a substituted derivative **3e** with similar results (Scheme 8).

Scheme 8. Final RCM Step



The results reported herein allow the rapid and stereoselective assembly of two unprecedented and interesting fluorinated scaffolds based on the dihydro- or tetrahydronaphthalene backbone, more specifically benzo-fused aminofluoroolefins and fluorinated 1,3-amino alcohols, respectively. The synthesis of the common substrates for both these families of compounds **10a−h** was achieved by means of our one-pot condensation/asymmetric/allylation/RCM procedure[10e] followed by a three-step reaction sequence consisting of deprotection/bromofluorination/reprotection reactions requiring a single purification, thus maximizing the efficiency of our approach. Fine-tuning the amount of base used for the elimination step was key for the discovery of these two divergent pathways. In addition, we have set up an alternative reaction sequence toward fluoroalkene containing 1-amino-1,2-dihydronaphthalene derivatives by reversing the reaction sequence. Furthermore, we have reported for the first time the synthesis of OFVBA. A synthetic procedure that allows us to overcome this molecule's instability is in progress in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03671.

DOI: 10.1021/acs.orglett.5b03671
Org. Lett. 2016, 18, 948−951

Experimental procedures, characterization of all new compounds, copies of HPLC chromatograms, and NMR spectra (^{1}H, ^{13}C, and ^{19}F) (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: pablo.barrio@uv.es.
*E-mail: santos.fustero@uv.es.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the Spanish MINECO (CTQ2013-43310) and Generalitat Valenciana (PROMETEOII/2014/073) for financial support. R.L. and D.M.S. thank the Spanish Government and the Generalitat Valenciana for predoctoral fellowships.

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(19) For optimization details, see the Supporting Information.

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DOI: 10.1021/acs.orglett.5b03671
Org. Lett. 2016, 18, 948–951