JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

# Late-Stage Deoxyfluorination of Alcohols with PhenoFluor

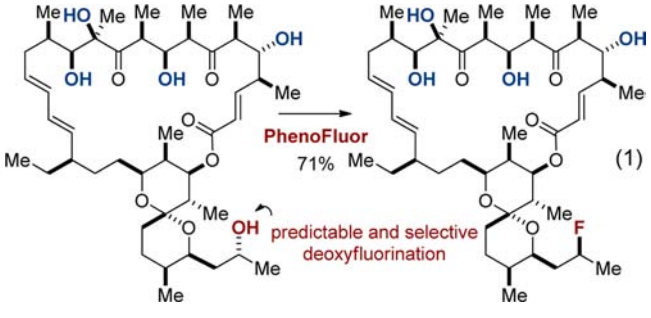
Filippo Sladojevich, Sophie I. Arlow, Pingping Tang, and Tobias Ritter*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

Supporting Information

**ABSTRACT:** An operationally simple protocol for the selective deoxyfluorination of structurally complex alcohols is presented. Several fluorinated derivatives of natural products and pharmaceuticals have been prepared to showcase the potential of the method for late-stage diversification and its functional group compatibility. A series of simple guidelines for predicting the selectivity in substrates with multiple alcohols is given.

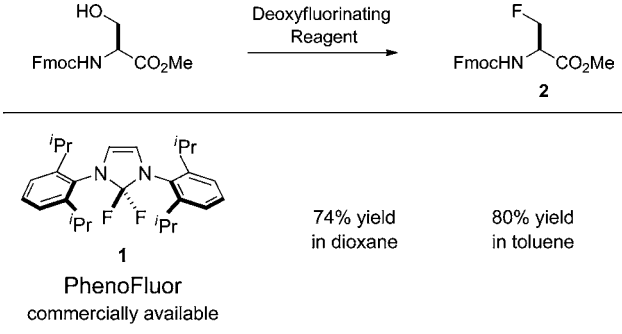
The selective modification of natural products and druglike molecules can rapidly generate new pharmaceutical candidates with potentially improved pharmacological profiles.[1] Late-stage fluorination[2] is particularly promising in this regard because incorporation of fluorine into molecules can increase their metabolic stability, bioavailability, and blood−brain barrier penetration.[3] However, late-stage fluorination is challenging, and to the best of our knowledge, no general late-stage aliphatic fluorination method is currently available. Here we report the first functional-group-tolerant aliphatic deoxyfluorination reaction of complex primary, secondary, and tertiary alcohols. Deoxyfluorination of structurally simple alcohols is known, and several reagents for deoxyfluorination have been described.[4,5] However, current deoxyfluorination methods are commonly characterized by limited functional group tolerance, side reactions such as elimination, and instability or explosion of the reagents upon heating.[4c,5a,6] The method presented herein (eq 1) employs commercially available PhenoFluor (**1**), a




crystalline, nonexplosive solid that does not suffer from competing side reactions to the extent that other deoxyfluorination reagents do. The conceptual advantage of PhenoFluor, beyond its better safety profile, is manifested in its chemoselectivity, which results in the ability to introduce fluorine selectively and predictably into complex small molecules with several hydroxyl groups, which has not been shown with other reagents.

PhenoFluor was originally developed for deoxyfluorination of phenols,[7] and we found that appropriate modification of the reaction conditions allows deoxyfluorination of aliphatic alcohols. Deoxyfluorination of alcohols can be accomplished with several commercially available reagents, such as DAST[5a] and Deoxo-fluor,[5b] but is normally not compatible with a variety of functional groups and is often plagued by elimination or other side reactions.[5a,6] Table 1 shows the utility of

**Table 1. Comparison of PhenoFluor with Other Commercially Available Deoxyfluorinating Reagents**[a]



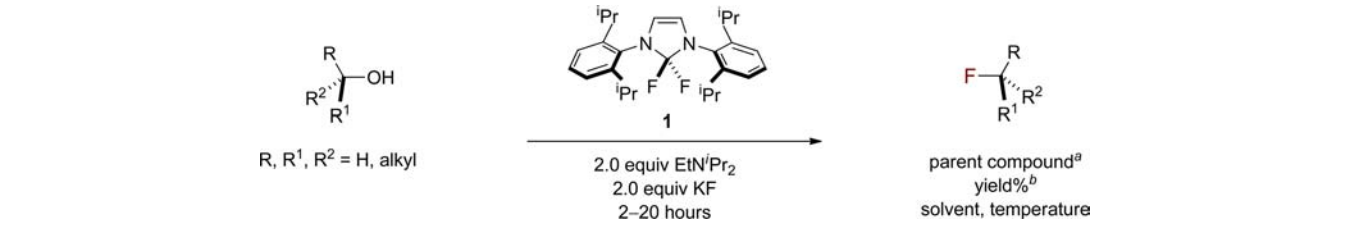

[a]Yields were determined by $^{19}$F NMR spectroscopy using 1-fluoro-3-nitrobenzene as an internal standard. [b]Best yield obtained from reactions run in toluene, in dioxane and under the optimized reaction conditions previously reported for the reagent (see the Supporting Information for details).

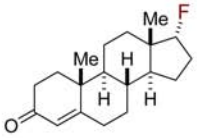
PhenoFluor compared with other commercially available deoxyfluorination reagents and illustrates the fact that PhenoFluor gives access to fluorinated molecules that are practically inaccessible by deoxyfluorination using other reagents. Fmoc-serine methyl ester was selected as a simple but challenging test substrate for evaluation. The $\beta$-hydroxy ester moiety of Fmoc-serine methyl ester is prone to formal

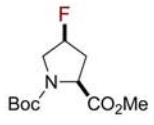
**Received:** December 22, 2012
**Published:** February 11, 2013

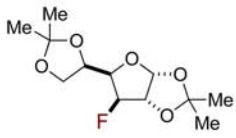
   dx.doi.org/10.1021/ja3125405 | J. Am. Chem. Soc. 2013, 135, 2470−2473

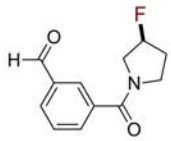
**Table 2. Late-Stage Deoxyfluorination of Alcohols with PhenoFluor**

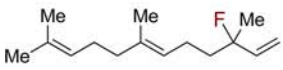




testosterone, **3**
88%
toluene, 80 °C


(2*S*,4*R*)-4-hydroxy-proline, **4**
92%
toluene, 80 °C

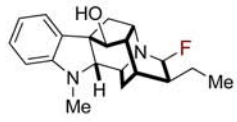

*D*-allofuranose, **5**
83%
toluene, 80 °C

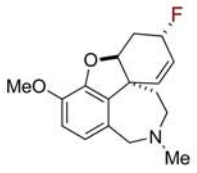

(±)-**6**
77%
toluene, 80 °C

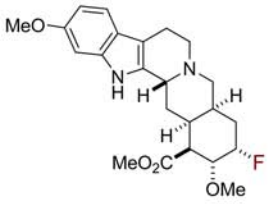

(±)-(*E*)-nerolidol, **7**
53%[c]
toluene, 80 °C

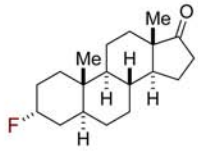

artemisinin, **8**
79%[d]
toluene, 80 °C

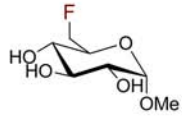

morphine, **9**
80%
$CH_2Cl_2$, 23 °C

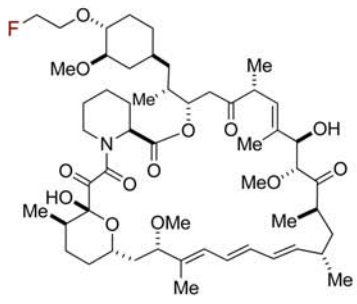

ajmaline, **10**
30%
$CH_2Cl_2$, 50 °C

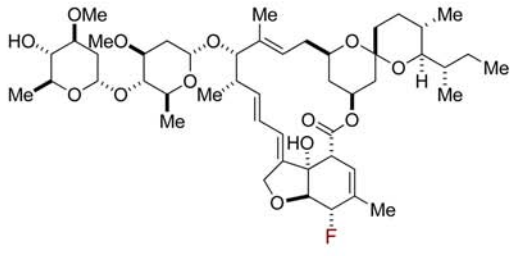

galantamine, **11**
80%, 10:1 dr
touene, 80 °C

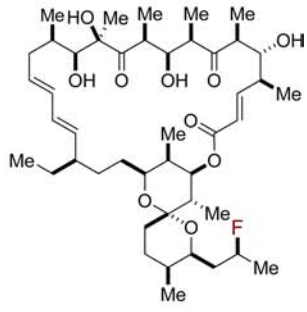

reserpine, **12**
82%
toluene, 80 °C


*epi*-androsterone, **13**
84%
toluene, 80 °C


methyl α-D-glucopyranoside, **14**
43%
dioxane, 80 °C


everolimus, **15**
83%[e]
$CH_2Cl_2$, 23 °C


ivermectin $B_{1a}$, **16**
41%
toluene 50 °C


oligomycin A, **17**
71%[e]
$CH_2Cl_2$, 23 °C to 0 °C

[a]The natural product/pharmaceutical used as the starting material or the natural product/pharmaceutical from which the starting material was derived. [b]Isolated yields of single compounds are shown. [c]A 16% yield of the corresponding primary allylic fluoride was isolated. [d]Deoxyfluorination with retention was observed. [e]No KF was used.

elimination of water when the hydroxyl group is converted into a leaving group, and the carbamate group can form the corresponding aziridine by intramolecular cyclization subsequent to alcohol activation; both of these side reactions were observed with the conventional reagents shown in Table 1. Evaluation of each reagent was performed in toluene, in dioxane, and under the optimized conditions previously reported for each reagent.[5a−e] Fluoroserine **2** was obtained at best in 11% yield with conventional deoxyfluorination reagents but could be obtained in up to 80% yield with PhenoFluor.

Deoxyfluorination of aliphatic alcohols with PhenoFluor can be carried out at room temperature, enabling fluorination of


dx.doi.org/10.1021/ja3125405 | *J. Am. Chem. Soc.* 2013, 135, 2470−2473

temperature-sensitive substrates. For example, for everolimus[8] (see **15**) or oligomycin A (see **17**), fluorination was performed at room temperature to avoid decomposition (Table 2). The addition of Hünig's base was beneficial to shorten the reaction time, and KF was found to reduce side products resulting from elimination but was not generally required for the reaction to proceed. The formation of reaction products resulting from elimination could also be reduced by increasing the reaction temperature from 23 to 80 °C when toluene was used as the solvent. For example, while the deoxyfluorination of testosterone (see **3**) and *epi*-androsterone (see **13**) proceeded at 23 °C, they were performed at 80 °C because elimination was found to be the main side reaction for *epi*-androsterone and testosterone at 23 °C. Appropriate reaction solvents in addition to toluene are dioxane and $CH_2Cl_2$, depending on the solubility of the alcohol substrate. Chiral secondary alcohols could typically be deoxyfluorinated with inversion without observed epimerization or elimination. In addition, secondary allylic alcohols afforded allylic fluorides consistent with an $S_N2$ mechanism and only small amounts (if any) of allylic fluorides consistent with an $S_N2'$ mechanism. Ketones and especially aldehydes are challenging substrates for deoxyfluorination reactions because they are often converted to the corresponding geminal difluorides,[4a] yet PhenoFluor can tolerate carbonyl functional groups (e.g., see **3**, **6**, and **13**).

Complex molecules, such as several of those depicted in Table 2, frequently contain more than one carbinol. Typically, PhenoFluor can discriminate between different carbinols and afford a single fluorinated analogue with synthetically useful selectivity; for example, a 71% yield of the fluorinated oligomycin A analogue **17** was isolated, despite the presence of five hydroxyl groups in oligomycin A (**18**) (Figure 1). We

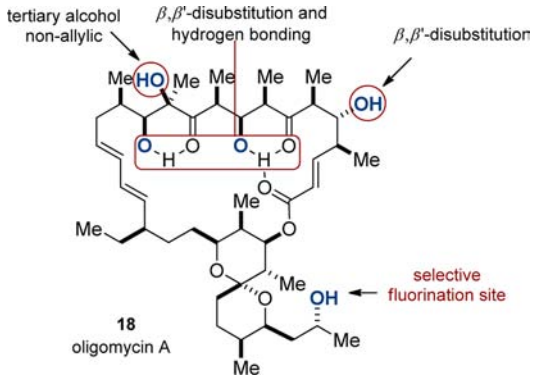



**Figure 1.** Rationale for the site-selective deoxyfluorination of oligomycin A (**18**).

observed several trends that enable the prediction of the fluorination site in the presence of several hydroxyl groups: (1) Primary alcohols are selectively deoxyfluorinated in the presence of secondary and tertiary alcohols. (2) Secondary alcohols react significantly slower or not at all when they are $\beta,\beta'$-dibranched, unless the secondary alcohol is allylic. (3) Tertiary alcohols do not react, unless they are allylic. (4) On the basis of previous observations,[7] hydroxyl groups engaged in hydrogen bonding are not reactive. For the substrates evaluated, these four guidelines were sufficient to predict the deoxyfluorination reactivity and selectivity correctly.

PhenoFluor is distinguished from other deoxyfluorination reagents such as DAST primarily through its better safety profile and higher chemoselectivity. The chemoselectivity of PhenoFluor enables access to complex fluorinated molecules; other deoxyfluorination reagents do not discriminate well between reactive functional groups. For example, DAST affords several (at least five) more fluorinated analogues upon reaction with **18** as a result of the indiscriminate reaction of DAST with secondary alcohols, including $\beta,\beta'$-substituted carbinols. The source of the differentiated chemoselectivity of PhenoFluor is not yet understood but likely is more complex than could be rationalized simply on the basis of its larger size compared with the other deoxyfluorination reagents. We have observed that unanticipated hydrogen bonding between the hydrogen atoms of the imidazoline ring of PhenoFluor and bifluoride is important for reactivity.[7] The better safety profile is another benefit of PhenoFluor. Several conventional reagents are unstable toward heat or even explosive. An exotherm of only 0.15 kcal·g$^{-1}$ was observed by differential scanning calorimetry (DSC) at PhenoFluor's decomposition temperature of 213 °C.

In conclusion, we have developed a general method for the selective, predictable, direct deoxyfluorination of complex alcohols. The substrate scope and functional group tolerance surpass those of any aliphatic fluorination reaction reported to date. One drawback of PhenoFluor is its molar mass of 427 g·mol$^{-1}$, which makes it a convenient reagent for subgram-and gram-scale reactions but a wasteful reagent for larger-scale reactions. We are currently investigating the potential of extending the reported method to late-stage $^{18}F$ radiolabeling[9] for positron emission tomography (PET) applications.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures, spectroscopic characterization for all new compounds, and details of the comparison of PhenoFluor with other commercially available reagents. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

ritter@chemistry.harvard.edu

### Notes

The authors declare the following competing financial interest(s): PhenoFluor is currently sold by Sigma-Aldrich and Strem and licensed by SciFluor Life Sciences. P.T. and T.R. have financial interest in PhenoFluor sales.

## ■ ACKNOWLEDGMENTS

We thank S. Huang (Harvard) for help with NMR data collection and structure elucidation, E. Lee (Harvard) for X-ray data collection and analysis, and the NIH (GM088237) and the European Community (Marie Curie IOF fellowship to F.S.) for financial support.

## ■ REFERENCES

(1) (a) Long, A. A. W.; Nayler, J. H. C.; Smith, H.; Taylor, T.; Ward, N. *J. Chem. Soc. C* **1971**, 1920−1922. (b) Lewis, C. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616−5619. (c) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461−477. (d) Butler, M. S. *Nat. Prod. Rep.* **2008**, *25*, 475−516. (e) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701−11706. (f) Balthaser, B. R.; Maloney, M. C.; Beeler, A. B.; Porco, J. A., Jr.; Snyder, J. K. *Nat. Chem.* **2011**, *3*, 969−973. (g) Jordan, P. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2907−2911. (h) Pathak, T. P.; Miller, S. J. *J. Am. Chem. Soc.*

**2012**, *134*, 6120−6123. (i) Fowler, B. S.; Laemmerhold, K. M.; Miller, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 9755−9761. (j) Voica, A.-F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 629−635.

(2) For examples of late-stage fluorination, see: (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661−1664. (b) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150−12154. For selected examples of di- and trifluoromethylation, see: (c) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411−14415. (d) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224−228. (e) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494−1497. (f) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95−99.

(3) (a) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803−819. (b) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (e) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470−477.

(4) For reviews of deoxyfluorination, see: (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561−2578. (b) Singh, R. P.; Meshri, D. T.; Shreeve, J. M. *Adv. Org. Synth.* **2006**, *2*, 291−326. (c) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305−321. (d) Al-Maharik, N.; O'Hagan, D. *Aldrichimica Acta* **2011**, *44*, 65−75.

(5) For DAST, see: (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574−578. For Deoxo-fluor, see: (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048−7054. For DFI, see: (c) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618−1619. For Xtal-fluor, see: (d) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050−5053. For Fluolead, see: (e) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199−18205. For other deoxyfluorinating reagents, see: (f) Yarovenko, N. N.; Raksha, M. A.; Shemanina, V. N.; Vasil'eva, A. S. *Zh. Obshch. Khim.* **1957**, *27*, 2246−2250. (g) Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377−3380. (h) Munyemana, F.; Frisque-Hesbain, A.-M.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 3077−3080.

(6) *Modern Fluoroorganic Chemistry*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

(7) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482−11484.

(8) For example, storage recommendations for everolimus are a temperature of −20 °C, exclusion of light, and the presence of BHT as a stabilizer, See: European Medicines Agency. Evaluation of Medicines for Human Use, London, 29 May 2009, Doc. Ref.: EMEA/533232/2009. http://www.ema.europa.eu/ema/ (accessed Dec 22, 2012).

(9) (a) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639−642. (b) Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456−17458.