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Selective Organic Synthesis

Metal Ion-Induced Large Fragment Deactivation: A Different Strategy for Site-Selectivity in a Complex Molecule

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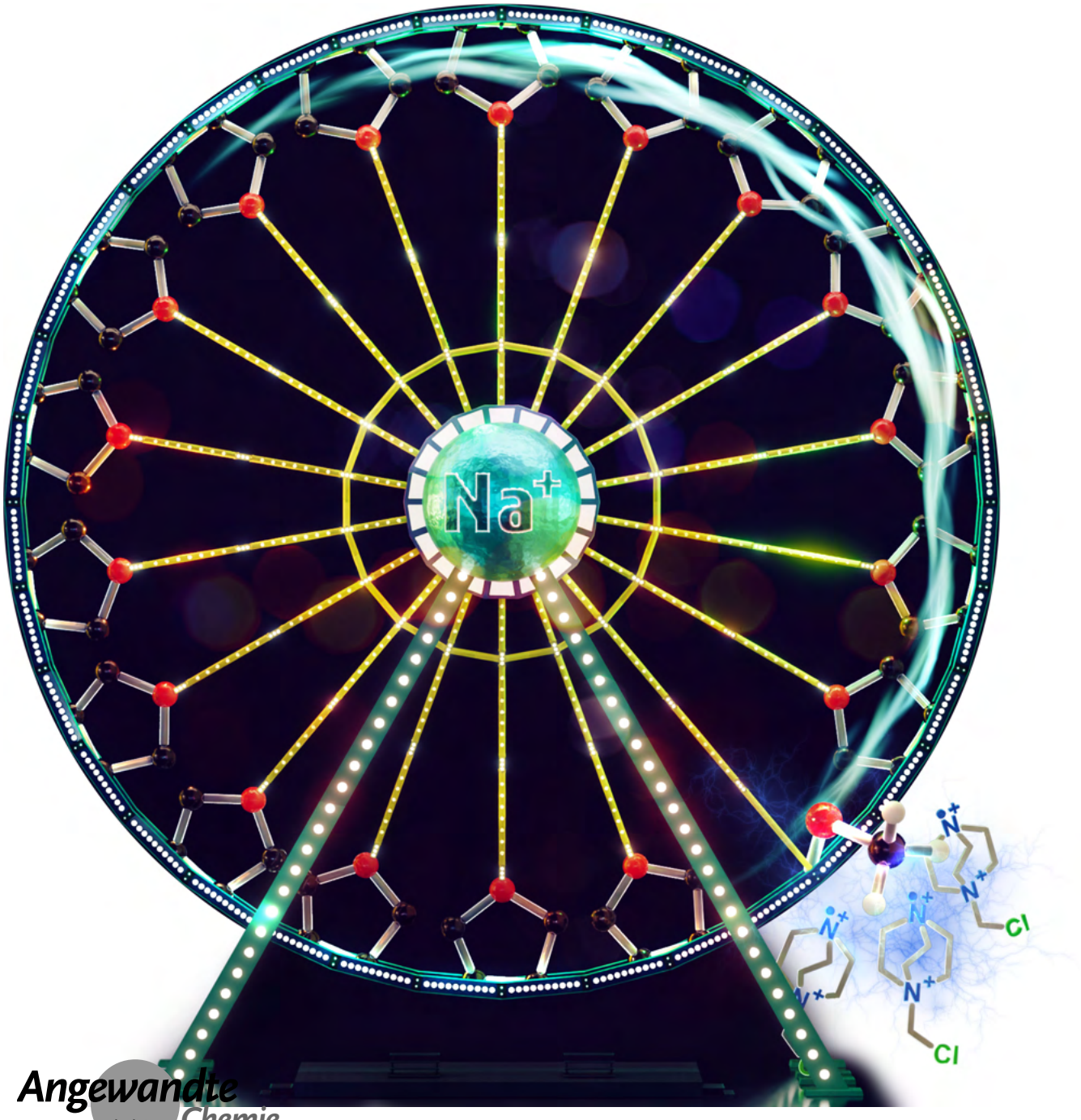

Abstract: Complex natural product functionalizations generally involve the use of highly engineered reagents, catalysts, or enzymes to react exclusively at a desired site through lowering of a select transition state energy. In this communication, we report a new, complementary strategy in which all transition states representing undesirable sites in a complex ionophore substrate are simultaneously energetically increased through the chelation of a metal ion to the large fragment we wish to neutralize. In the case of an electrophilic, radical based fluorination reaction, charge repulsion (electric field effects), induced steric effects, and electron withdrawal provide the necessary deactivation and proof of principle to afford a highly desirable natural product derivative. We envisage that many other electrophilic or charge based synthetic methods may be amenable to this approach as well.

Imagine a large molecule that we wish to functionalize at a particular site. Unfortunately, nonselective reactivity at random sites is observed instead. How would one go about blocking functionalization at *all* the undesired sites *en masse*? Modern organic chemistry presents few solutions to such a challenging and vexing problem,[1] although one stands out as a successful strategy. In general, evolution tends towards complexity and specialized functionality;[2] a similar model predominates in modern synthetic organic methods for late-stage functionalizations.[3] Complex natural products are believed to merit the development of highly engineered reagents,[4] catalysts,[5] or even enzymes[6] to react exclusively at a desired site through lowering of a select transition state energy.[7]

Recently, we questioned if this approach could be inverted. More specifically, could *all* transition states representing undesirable sites in a complex substrate be simultaneously energetically increased, permitting a "less-evolved" reagent to functionalize a desired C–H bond (Figure 1)? If the substrate is an ionophore, a novel solution comes to mind in the chelation of a metal ion to the fragment we wish to neutralize. In the case of an electrophilic reaction, charge repulsion,[8] induced steric effects (perhaps), and electron withdrawal[9] will theoretically provide the necessary deactivation and proof of principle.

Polyether antibiotics are one such class of complex, naturally derived compounds.[10] In the presence of cations, they bind in crown ether-like fashion to sequester charged metals and enhance their lipophilicity across cellular membranes.[10] In this delocalized cradling of charge, we envisioned an illustrative means of selectivity. Fragments of a molecule we wished to neutralize could be blocked through metal ion chelation, whereas an uncoordinated region would remain susceptible to functionalization (Figure 2). A large metal ion would block the most sites; a smaller metal ion would block fewer, leaving the inherent reactivity of a free site to dictate the outcome.

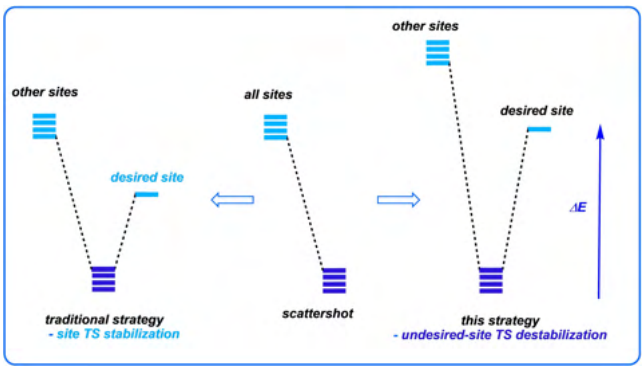

Figure 1. Two strategies for site selectivity.

Of the over 120 known polyether ionophores,[11] monensin A (**1**) was selected to test the concept due to its commercial availability, pharmaceutical relevance, and ubiquity in the literature.[12] In turn, our prognostication of site-selective reactivity was guided in large part by substantial existing crystal structure data on **1** and related derivatives.[12] We made the assumption that this data would map onto solution phase behavior; given the high binding affinities of certain metal ions for **1**,[13] we viewed this as a reasonable

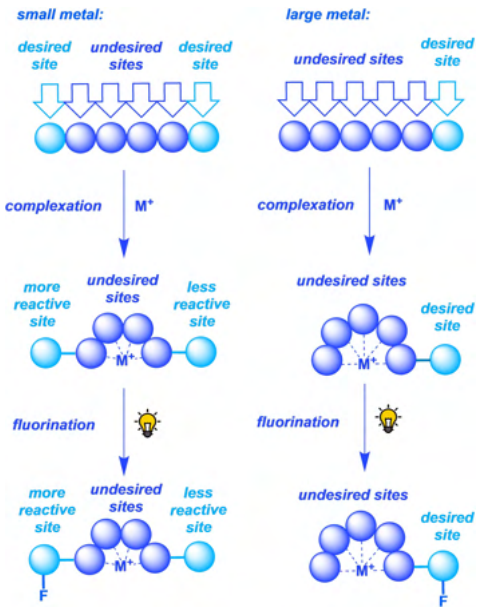

Figure 2. General approach.

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deduction. Several ester derivatives of **1** have been synthesized as well,[14] and we were also drawn to monensin A methyl ester (**3**) for its established ability to complex monovalent cations with 1:1 stoichiometry[15] and its solubility in polar organic solvents necessary for the reaction. Furthermore, we wished to probe whether selectivity observed in reactions with **1** would be conserved upon modification of the molecule's carboxylic acid terminus.

In experiments with metal cations in acetonitrile, our solvent of choice, Pointud and co-workers found that the association constants with **1** vary in the order of $Na^+ > Li^+ > K^+ > Rb^+ > Ag^+ > Cs^+$.[13] We selected sodium and lithium ions to template our reactions owing to their considerably higher binding affinities with **1** relative to the other alkali metals.[13] In this respect, results arising from a difference in ionic radius would not be misattributed to a difference in ion affinity. Moreover, both cations have been crystallized with **1** and appear in the seminal structures presented by Huczyński and co-workers.[16] Two crystal structures for a monensin ester have also been reported, including the 1-naphthylmethyl ester of monensin with sodium perchlorate, as well as the aquo-lithium 1-naphthylmethyl ester of monensin perchlorate.[17] By working with Na^+ and Li^+, we were able to draw direct analogies to these structures when interpreting patterns of selectivity in the modification of **3**.

Perhaps most importantly, we utilized an electrophilic mechanism dependent on a relatively unspecialized and general-purpose fluorinating reagent.[18] This helped ensure that any selectivity observed during the fluorination of **1** and **3** would be an artifact of our nonsite destabilization and localized effects. By forming C–F bonds, we were also easily able to screen for selectivity by ^{19}F NMR spectroscopy.

The mechanism employed in this work is one developed and researched by our group.[19] Selectfluor radical dication (SRD) is generated under photochemical conditions to initiate a highly electrophilic variant of hydrogen atom transfer (HAT, Figure 3, **a**). We anticipated that metal binding to the substrate will raise the HAT barrier substantially through charge repulsion and related effects. The resulting radical is subsequently fluorinated with Selectfluor to regenerate SRD and perpetuate a chain reaction.

Our first goal was to establish that the fluorination of **1** proceeds indiscriminately in the absence of cations. The backbone of **1** is replete with hydroxy groups, α-ethereal positions, and C–H bonds well within the ≈100 kcal/mol HAT capability of SRD;[20] lone pairs of electrons can also serve as local directing groups.[18] We have investigated the connection between each of these structural features and C–F bond formation in independent studies[21] but predicted that their confluence in **1** would lead to "scattershot" fluorination (Figure 3, **b**). Unsurprisingly, running the reaction with **1** under salt-free conditions resulted in a multitude of fluorinated products by ^{19}F {^1H} NMR (Figure 4). No single product was produced in isolable quantities.

We then subjected **1** to radical fluorinating conditions (Selectfluor, 10 mol % benzil, 400 nm hv, MeCN, 25 °C) after allowing it to stir in a solution of excess $NaBF_4$ for at least one hour. To our satisfaction, the single monofluorinated product **2** was generated (^{19}F NMR yield, see SI); optimization led to 53 % yield (95 % based on remaining starting material). Although smearing on silica prevented direct isolation of this product (full characterization was accomplished through simple derivatization, also see SI), the sharp triplet observed by ^{19}F NMR made clear that fluorination occurred at the methyl ether position (Figure 4), generating **2**. Note that **2** was unobserved in the control reaction with apo monensin, constituting a total switch in product profile upon metal complexation.

Even more gratifying was the agreement between substitution at this site and the crystal structure of **1**-carboxylate with Na^+; sodium-bound **1** is shown to adopt a quasi-macrocyclic conformation with the methyl ether site conspicuously exposed (Figure 5).[16a] Each of the rings along the skeleton of **1**, in contrast, is coordinated to Na^+ through an oxygen atom. We therefore attribute this extreme selectivity to the aforementioned generalized molecular deactivation; cation-bound fragments of **1** are precluded from reacting with SRD due to electrostatic and steric effects, whereas the exposed region remains susceptible to selective HAT reactivity. Predicting that this selectivity should be maintained using a different HAT-based methodology, we also fluorinated sodium-bound **1** using Selectfluor

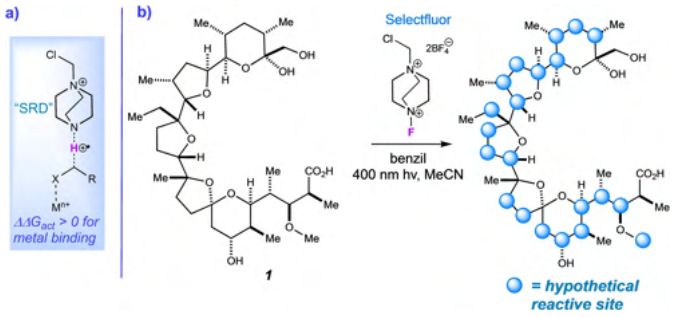

Figure 3. Anticipated "scattershot" fluorination of apo-monensin (**1**).

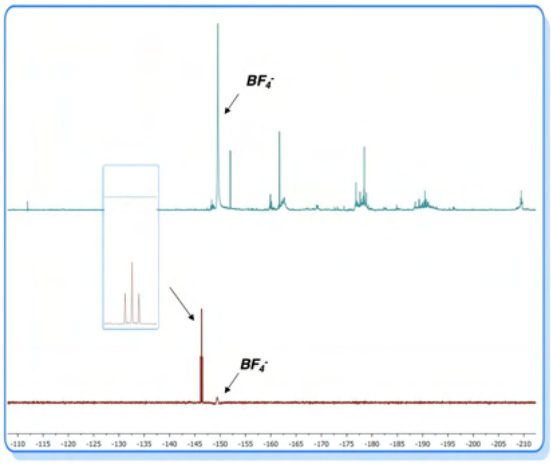

Figure 4. Apo-**1** (top, ^{19}F {^1H} NMR in $CDCl_3$) fluorinates indiscriminately. Na^+-**1** (bottom, ^{19}F NMR in $CDCl_3$) reacts with complete selectivity at an otherwise inaccessible site.

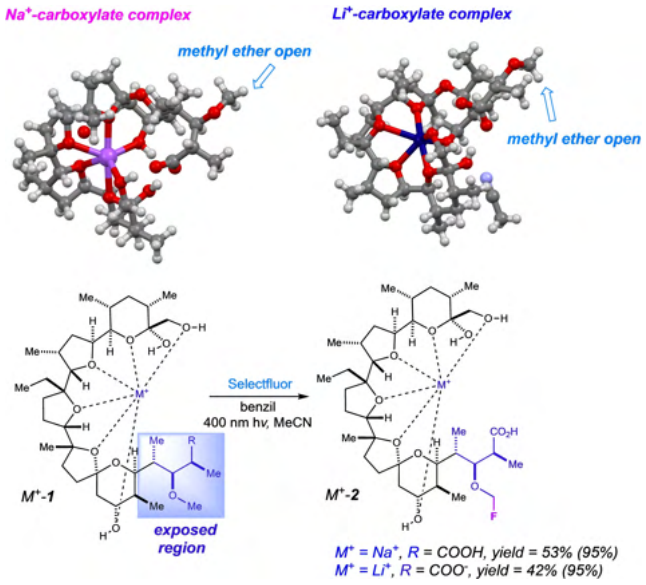

Figure 5. Fluorination of cation-bound **1** correlates to existing carboxylate crystal structures. ^{19}F NMR yields are reported. Yields based on remaining starting material are shown in parenthesis.

under previously developed electrochemical conditions.[22] Methyl ether fluoride **2** was selectively generated in higher yield (57 %), possibly owing to the dual role served by excess $NaBF_4$ as supporting electrolyte.[23]

The dramatic effect on selectivity in the presence of sodium ion can be understood from Monte Carlo conformational searches (MCCS) of Na^+-**1** and SRD.[24] The lowest energy conformer identified (Figure 6a) was found to represent a pseudo-transition state or precomplex. Notably, positive charge pervades the backbone of **1** in the calculated electrostatic potential surface (Figure 6b) but fails to congregate on the targeted methyl ether arm. Furthermore, the computed highest occupied molecular orbital (HOMO, Figure 6c) is confined to the methyl ether, where SRD is poised for HAT reactivity.

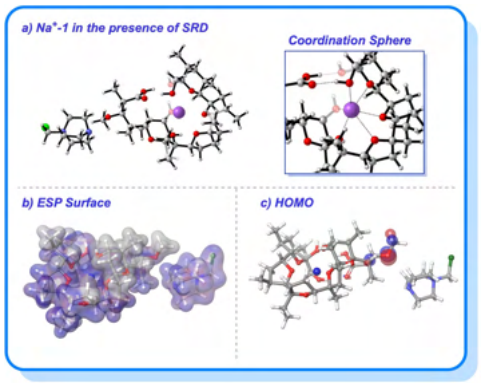

Figure 6. a) Lowest energy conformer optimized at density functional theory (DFT) for Na^+-**1** in the presence of SRD. b) The calculated electrostatic potential surface (ESP) of the low energy conformer. c) The computed HOMO of the low energy conformer.

These results are buttressed by our replications of the photochemical experiment using Li^+ (Figure 5). In the crystal structure of Li^+ with **1**-carboxylate, the methyl ether site is also completely exposed[16b] and, in keeping with this observation, running the reaction with $LiClO_4$ (1 eq.) and Li_2CO_3 (0.5 eq.) affords the same selectivity as with $NaBF_4$. The addition of base was necessary to produce this result - reviewing crystal structure data, the hydroxy-adorned terminal ring of cation-bound **1** "cinches" the conformation of the structure through hydrogen bonding interactions with the carboxylic acid portion of the molecule.[16b] We suspected that the diminutive ionic radius of Li^+ relative to Na^+ required potentiated H-bonding interactions to deactivate the distal ring to fluorination. Formation of the carboxylate with base, and creating a better match to the crystal structure of **1** with Li^+, achieved absolute selectivity. Replications of the $NaBF_4$ experiment with $KClO_4$ as a source of cation, on the other hand, resulted in both poor conversion and selectivity, corresponding to the weaker binding affinity of **1** for K^+ in acetonitrile.[13] Similarly, fluorination in the presence of $AgNO_3$ resulted in background scattershot reactivity. With an established proclivity for redox activity with Selectfluor,[25] Ag(I) is found to be an unreliable cationic deactivator.

Proceeding with the insight that selectivity can be mapped using crystal structures, we focused our next efforts on monensin methyl ester **3**. Similar to substrate **1**, fluorination in the presence of excess $NaBF_4$ resulted in methyl ether fluoride **5** (48 % yield), agreeing with the binding observed in the crystal structure of the 1-naphthylmethyl ester of monensin with sodium perchlorate.[17] Note that we make the assumption that the naphthylmethyl ester and methyl ester have similar complexed forms in solution; experiment seems to bear this out. Due to a better ability to run on silica, **5** was isolated by standard preparatory HPLC and found to exhibit characteristic diastereotopic methyl ether fluoride ^1H NMR signals.[26]

Low energy MCCS for substrate **3** were also found to be predictive of selectivity. In the apo form, SRD binds in a concave pocket created by **3** as a surrogate for the metal ion; precedent shows that ammonium ions also bind to the monensin backbone in such a fashion (Figure 7).[27] Thus, we can conclude that scattershot fluorination would be favored, as is the case. Conversely, SRD clusters in the vicinity of the methyl ether in sodium-bound **3** – thus we expect a selective reaction in the presence of $NaBF_4$.

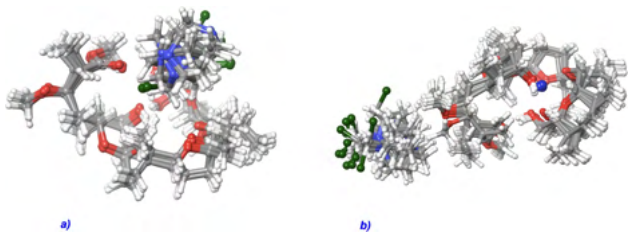

Figure 7. Low energy cluster of the complexes of SRD with a) apo-**3** and b) Na^+-**3** (OPLS4 force field, MacroModel program).

In a seemingly aberrant case, photochemical fluorination of **3** using $LiClO_4$ furnishes a new major product: tertiary fluoride **4** at the opposing extremity of the monensin methyl ester backbone (Figure 8). Once again, crystal structure data provide a simple rationalization of this result. In the structure of the 1-naphthylmethyl ester of monensin with Li^+, the two termini of **3** are now shown to be unbound, with an aquo ligand occupying a coordination site on Li^+.[17b] With this additional cyclic ether liberated, fluorination is able to proceed to target a distal tertiary site. Substitution at the methyl ether only features as a minor product in the fluorination of **3** with $LiClO_4$, indicating that the natural reactivity of the opposite terminus overrides methyl ether reactivity.

The relevance of our approach is clear when considering the ability of monensin-metal binding to withstand biological conditions.[28] It occurred to us that the metabolism of sodium-bound monensin compounds could follow a similar reactivity pattern to the one we observed, namely the selective oxidation and hydrolysis of the methyl ether by an electrophilic, iron-based oxidase; this is in fact the case.[29] Testing of rat and steer feces, for example, resulted in the identification of six monensin A metabolites, five of which involve the cleavage of the methyl ether (three examples **6**–**8** in Figure 9, top).[30] A simple MCCS simulation of this HAT reaction using electrophilic heme oxo radical cation **9** as a model shows that it should also be selective in the case of Na^+-**3** (a), whereas the reaction of apo-**3** should lead to a different outcome (b). Evidently, our large fragment deactivation strategy targets a site of great physiological import.

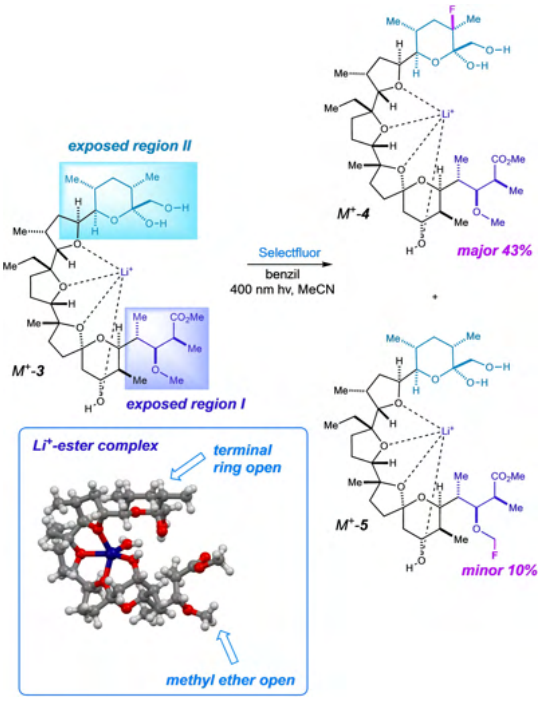

Figure 8. Li^+-**3** inverts selectivity to the opposite terminus. $^{19}F\{^1H\}$ NMR yields are reported.

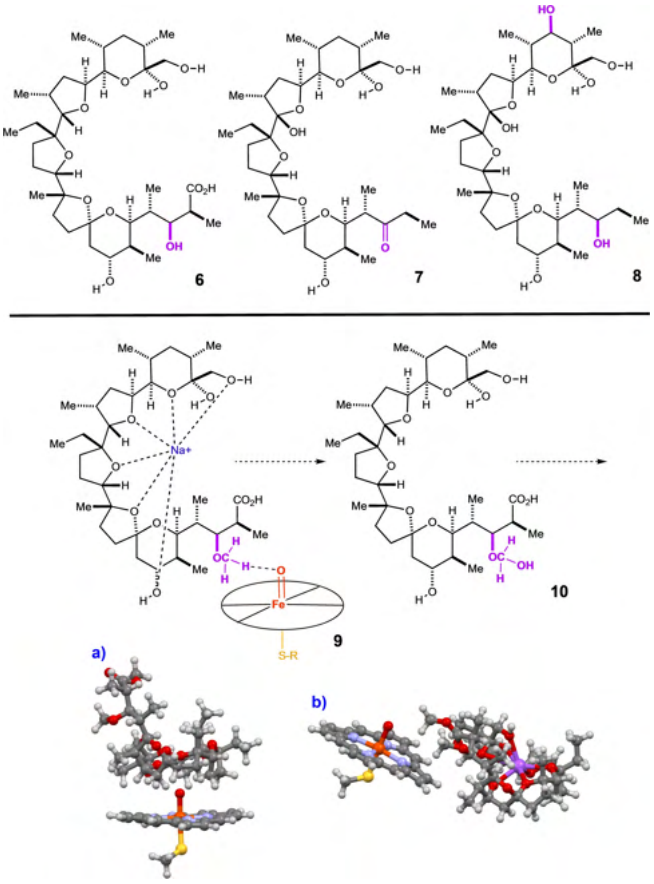

Figure 9. Top. Correlation of metabolites with this study. Bottom. Putative enzymatic reaction of **1**. a) Low energy conformer from MCCS of oxo-heme sulfide radical cation with apo-**3**. b) Low energy conformer from MCCS of oxo-heme sulfide radical cation with Na^+ −**3**.

Emergent research shows that monensin and its derivatives exhibit potent anticancer properties.[31] Even so, the use of monensin compounds for therapeutic purposes has been largely discounted owing to their ephemeral half-life.[32] Potential solutions to this drawback have focused primarily on developing a competent drug delivery system to accompany monensin in vivo.[33] The judicious installation of fluorine, however, is frequently employed in medicinal chemistry to extend the half-life of drug candidates that metabolize too rapidly.[34] It stood to reason that compound **5**, fluorinated at the methyl ether position, might also benefit from improved metabolic stability. To be sure, parent compound **3** (1 μM) was found to be extremely unstable when incubated with rat liver microsomes, falling below detectable levels at an early sampled time point of 5 min. (Figure 10). A significant amount of methyl ether fluoride **5**, on the other hand, remained at 5 min. and could still be detected at 15 min. This represents a significant, albeit unoptimized, improvement to the in vitro pharmacokinetics of **3**. Tertiary fluoride **4** enjoyed no such metabolic resilience, emphasizing the biological significance of having targeted the methyl ether.

We have demonstrated a new approach to the selective modification of a complex and biologically active natural

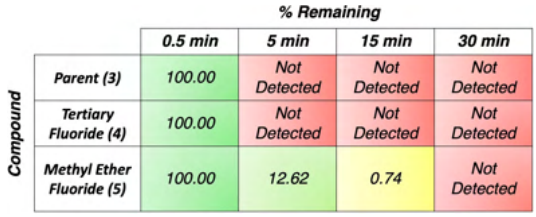

Figure 10. Fluorination of **3** at the methyl ether position increases stability in rat liver microsomes.

product using alkali metal ions to block a large molecular fragment. In contrast to the current ethos of late-stage functionalization, our concept relies on the use of a general-purpose fluorinating reagent to target a limited number of unblocked sites rather than a highly evolved reagent choosing between all sites on an entire molecule. Furthermore, we have proven that selectivity can be anticipated by existing crystal structure data and correlated to metabolic activity from in vivo studies. Similarly, our approach was found to improve the metabolic stability of a potential drug candidate in vitro. We believe this pairing of cationic charge with electrophilic reactions can be extended to other polyether ionophores and natural products, providing a complementary strategy for the selective functionalization of complex molecules. We also believe this strategy will be especially utilitarian for modifications proceeding through charged intermediates. The scope of this principle will be explored in works to follow.

Supporting Information

The authors have cited additional references within the Supporting Information.[35–36]

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Large Fragment Deactivation · Molecular Blocking · Radical Fluorination · Scattershot Reaction · Site-Selectivity

[1] a) L. Guillemard, N. Kaplaneris, L. Ackermann, J. Johansson, *Nat. Chem. Rev.* **2021**, *5*, 522–545; b) J. Börgel, T. Ritter, *Chem* **2020**, *6*, 1877–1887; c) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576; d) A. A. Bastian, A. Marcozzi, A. Herrman, *Nat. Chem.* **2012**, *4*, 789–793.
[2] C. Adami, C. Ofria, T. C. Collier, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 4463–4468.
[3] a) P. A. Lichtor, S. J. Miller, *Nat. Chem.* **2012**, *4*, 990–995; b) C. R. Shugrue, S. J. Miller, *Chem. Rev.* **2017**, *117*, 11894–11951.
[4] V. Mataoušek, J. Václavík, P. Hájek, J. Chaerpentier, Z. E. Blastik, E. Pietrasiak, A. Budinská, A. Togni, P. Beier, *Chem. Eur. J.* **2016**, *22*, 417–424.
[5] a) C. A. Lewis, S. J. Miller, *Angew. Chem. Int. Ed.* **2006**, *45*, 5616–5619; b) T. P. Pathak, S. J. Miller, *J. Am. Chem. Soc.* **2012**, *134*, 6120–6123.
[6] E. J. Craven, J. Latham, S. A. Shepherd, I. Khan, A. Diaz-Rodriguez, M. F. Greaney, J. Micklefield, *Nat. Catal.* **2021**, *4*, 385–394.
[7] a) F. D. Toste, M. S. Sigman, S. J. Miller, *Acc. Chem. Res.* **2017**, *50*, 609–615; b) J. Hwang, B. Q. Mercado, S. J. Miller, *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2113122118.
[8] D. A. Klumpp, *Chem. Eur. J.* **2008**, *14*, 2004–2015.
[9] R. D. Chambers, M. Parsons, G. Standford, E. Thomas, J. Trmcic, J. S. Moilliet, *Tetrahedron* **2006**, *62*, 7162–7167.
[10] D. A. Kevin II, D. F. Meijo, M. T. Hamman, *Expert Opin. Drug Discovery* **2009**, *4*, 109–146.
[11] C. J. Dutton, B. J. Banks, C. B. Cooper, *Nat. Prod. Rep.* **1995**, *12*, 165–181.
[12] J. Rutkowski, B. Brzezinski, *BioMed Res. Int.* **2013**, 162513.
[13] Y. Pointud, C. Bernard, S. Touzain, L. Astier, B. Sabatier, J. Julliard, *J. Solution Chem.* **1997**, *26*, 479–495.
[14] A. Huczyński, J. Stefańska, P. Przybylski, B. Brzezinski, F. Bartl, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2585–2589.
[15] A. Huczyński, P. Przybylski, B. Brzezinki, F. Barti, *Biopolymers* **2006**, *81*, 282–294.
[16] a) A. Huczyński, M. Ratajczak-Sitarz, A. Katrusiak, B. Brzezinski, *J. Mol. Struct.* **2007**, *832*, 84–89; b) A. Huczyński, M. Ratajczak-Sitarz, A. Katrusiak, B. Brzezinski, *J. Mol. Struct.* **2007**, *871*, 92–97.
[17] a) A. Huczyński, J. Janczak, B. Brzezinski, *J. Mol. Struct.* **2012**, *1030*, 131–137; b) A. Huczyński, J. Janczak, B. Brzezinski, *J. Mol. Struct.* **2011**, *985*, 70–74.
[18] a) We have found Selectfluor to fluorinate selectively through a radical chain process when a fairly rigid lone pair containing functional group is there to anchor it. However, its selectivity drops drastically in complex molecules with many such groups. For a recent Selectfluor review: K. Yang, M. Song, A. I. M. Ali, S. M. Mudassir, H. Ge, *Chem. Asian J.* **2020**, *15*, 729–741; b) In contrast to our approach, metal catalyst complexation with carbonyl moieties has been leveraged to selectively template ortho-substitution in aromatic compounds: X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 7416–7417.

[19] F. Ghorbani, S. A. Harry, J. N. Capilato, C. R. Pitts, J. Joram, G. N. Peters, J. D. Tovar, I. Smajlagic, M. A. Siegler, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2020**, *142*, 14710–14724.
[20] F. J. A. Troyano, K. Merkens, A. Gómez-Suárez, *Asian J. Org. Chem.* **2020**, *9*, 967–1086.
[21] a) S. A. Harry, M. R. Xiang, E. Holt, A. Zhu, F. Ghorbani, D. Patel, T. Lectka, *Chem. Sci.* **2022**, *13*, 7007–7013; b) J. N. Capilato, C. R. Pitts, R. Rowshanpour, T. Dudding, T. Lectka, *J. Org. Chem.* **2020**, *85*, 2855–2864.
[22] E. Holt, M. Wang, S. A. Harry, C. He, Y. Wang, N. Henriquez, M. R. Xiang, A. Zhu, F. Ghorbani, T. Lectka, *J. Org. Chem.* **2023**, *88*, 2257–2560.
[23] L. C. Portis, J. C. Roberson, C. K. Mann, *Anal. Chem.* **1972**, *44*, 294–297.
[24] a) H. Kim, *J. Phys. Chem. B* **2004**, *108*, 11753–11759; b) C. Ranghino, S. Romano, J. M. Lehn, G. Wipff, *J. Am. Chem. Soc.* **1985**, *107*, 7873–7877; c) D. W. Lim, S. A. Chyun, M. P. Suh, *Angew. Chem.* **2014**, *126*, 7953–7596.
[25] a) J. B. Roque, Y. Kuroda, L. T. Göttemann, R. Sarpong, *Science* **2018**, *361*, 171–174; b) J. D. Galloway, D. N. Mai, R. D. Baxter, *J. Org. Chem.* **2019**, *84*, 12131–12137.
[26] See 1-(Fluoromethoxy)-2,3-dihydro-1H-indene: Y. Liu, L. Lu, Q. Shen, *Angew. Chem.* **2017**, *129*, 10062–10066.
[27] K. Maruyama, H. Sohmiya, H. Tsukube, *J. Chem. Soc. Chem. Commun.* **1989**, 864–865.
[28] H. H. Mollenhauer, D. J. Morré, L. D. Rowe, *Biochim. Biophys. Acta Biomembr.* **1990**, *1031*, 225–246.
[29] a) C. Nebbia, L. Ceppa, M. Dacasto, C. Nachtmann, M. Carletti, *J. Vet. Pharmacol. Ther.* **2001**, *24*, 399–403; b) D. O'Hagan, *Nat. Prod. Rep.* **1995**, *9*, 447–479.
[30] A. Donoho, J. Manthey, J. Occolowitz, L. Zornes, *J. Agric. Food Chem.* **1978**, *26*, 1978.
[31] a) S. S. Kocoglu, C. Oy, M. Secme, F. B. Sunay, *Clin. Transl. Sci.* **2023**, *16*, 1725–1735; b) A. Urbaniak, M. R. Reed, B. Heflin, J. Gaydos, S. Piña-Oviedo, M. Jędrzejczyk, G. Klejborowska, N. Stępczyńska, T. C. Chambers, A. J. Tackett, A. Rodriquez, A. Huczyński, R. L. Eoff, A. M. MacNicol, *Biomed. Pharmacother.* **2022**, *153*, 113440; c) X. Wang, W. Wu, Z. Zhang, C. Ma, T. Wu, S. Tang, Z. Zeng, S. Huang, C. Gong, C. Yuan, L. Zhang, Y. Feng, B. Huang, W. Liu, B. Zhang, Y. Shen, W. Luo, X. Wang, B. Liu, Y. Lei, Z. Ye, L. Zhao, D. Cao, L. Yang, X. Chen, R. C. Haydon, H. H. Luu, B. Peng, X. Liu, T.-C. He, *Sci. Rep.* **2018**, *8*, 17914.
[32] T. Griffin, M. E. Rybak, L. Recht, M. Singh, A. Salimi, V. Raso, *J. Natl. Cancer Inst.* **1993**, *85*, 292–298.
[33] a) M. Singh, A. J. Ferdous, N. Kanikkannan, G. Faulkner, *Eur. J. Pharm. Biopharm.* **2001**, *52*, 13–20; b) M. S. Shaik, O. Ikediobi, V. D. Turnage, J. McSween, N. Kanikkannan, M. Singh, *J. Pharm. Pharmacol.* **2001**, *53*, 617–627.
[34] P. Shah, A. D. Westwell, *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540.
[35] a) M. J. O. Anteunis, N. A. Rodios, *Bioorg. Chem.* **1978**, *7*, 47–55.
[36] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.

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