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Remodeling of the Natural Product Fumagillol Employing a Reaction Discovery Approach

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Abstract

In search for new biologically active molecules, diversity-oriented synthetic (DOS) strategies break through the limitation of traditional library synthesis by sampling new chemical space. Many natural products can be regarded as intriguing starting points for DOS, wherein stereochemically rich core structures may be reorganized into chemotypes which are distinctly different from the parent structure. Ideally such transformations should be general and involve few steps in order to be suited for library applications. With this objective in mind, the highly oxygenated natural product fumagillol has been successfully remodeled in several ways utilizing a reaction discovery-based approach. In reactions with amines, excellent regiocontrol in a *bis*-epoxide opening/cyclization sequence can be obtained by size-dependent interaction of an appropriate catalyst with the parent molecule, forming either perhydroisoindole or perhydroisoquinoline products. Perhydroisoindoles can be further remodeled by cascade processes to afford either morpholinone or bridged 4,1-benzoxazepine-containing structures.

In order to identify pharmacological tools for biological processes, compound discovery must expand beyond the sp^2 -dominated synthetic libraries common in biological screening.¹ Diversity-oriented libraries have been demonstrated to occupy areas of chemical space not normally accessed by more traditional planar, heterocyclic libraries.^{2–4} One approach to access increasingly diverse libraries would employ natural products as starting scaffolds. A number of studies have exploited natural products as starting materials, including use of α -santonin^{5–7} and (–)-shikimic acid^{8,9} to identify biologically active molecules including 5-lipoxygenase inhibitors and aurora A kinase ligands. Other methods have focused on altering the core framework of natural products to create small collections of structurally unique compounds. A method involving catalytic, site-selective derivatization of complex

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Author contributions

B.R.B. and M.C.M. carried out the experimental work. A.B.B., J.A.P., Jr., and J.S.K. provided oversight. B.R.B., J.A.P., Jr., and J.S.K. conceived experiments and wrote the manuscript.

Additional information

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natural products (*e.g.* erythromycin) has been demonstrated by the Miller group at Yale.^{10,11} In another study, the macrocyclic diterpenoid lathyrane was converted into a small collection of polycyclic structures using transannular reactions.¹² The Miller group from Notre Dame has incorporated oxazine heterocycles into natural products bearing 1,3-butadiene subunits employing iminonitroso Diels-Alder cycloadditions.^{13,14}

Further evolution of these ideas would involve the creation of a diverse library of remodelled structures derived from a natural product, each one significantly different from the parent compound. Transformations utilized should allow for the incorporation of new functionality and ideally be carried out in a single-step or tandem processes. We therefore initiated a reaction discovery-based approach^{15–18} that meets these criteria employing a readily available natural product as a starting point for chemically diverse library synthesis (Figure 1a). The highly oxygenated natural product fumagillol (**2**) was chosen as the reactivity and proximity of the two epoxides present site(s) for potential chemistry, while the hydroxyl and alkene groups offer additional functionality for further diversification. Crude fumagillin (**1**), a natural product which is readily available from the fermentation broth of *Aspergillus fumigatus* and can be hydrolyzed to fumagillol (**2**) (see Supplementary Information),^{19,20} has generated significant interest as both a synthetic target²¹ and for its anti-angiogenic properties.^{22–24} We envisioned a series of tandem processes which could remodel fumagillol into novel chemotypes as dictated by either by catalyst or reaction partner choice. Herein, we report our initial studies aimed at remodeling fumagillol through Lewis acid-promoted addition of amines.

Results and Discussion

A reaction screen^{15,16} was first undertaken to explore sequential aminolyses of the 1,4-*bis*-epoxide. We anticipated that the sequence would be initiated at the spirocyclic epoxide, thereby mimicking the reactivity of fumagillin with aminopeptidase MetAP-2, the putative mode of its antiangiogenic activity.²³ An initial reaction screen (see Supporting Figures 1–5) with twelve Lewis acids and four amines resulted in the conversion of the *bis*-epoxide motif into perhydroisoindole (**3**)^{25–27} and/or perhydroisoquinoline (**4**),^{28–30} compounds which were identifiable through several characteristic signals in ¹H NMR spectra. Best results were obtained using *p*-anisidine and a metal triflate catalysis. Preliminary optimization of this transformation demonstrated that 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as proton scavenger significantly improved yields, presumably by buffering adventitious triflic acid.^{31,32} Several metal triflates were subsequently investigated in a second screen and a linear correlation was found between the atomic radius of the metal catalyst and the distribution of isomeric products (Figure 1b). As metal size increased, perhydroisoindole product **3** was increasingly favored. Lanthanum triflate proved to be optimal for production of **3** with >95:5 regioselectivity (entry 2). Conversely, the smaller, bivalent-metal Zn(OTf)₂ favored formation of perhydroisoquinoline **4** (entry 8, 13:87), thereby allowing access to either isomer simply by changing the catalyst.^{33–35} In the absence of a catalyst, no reaction occurred and fumagillol was fully recovered.

Further optimization using La(OTf)₃ and Zn(OTf)₂ catalysts was next pursued. The transformations were robust and did not require inert atmosphere, nor special precautions for

anhydrous solvent. Other nonpolar solvents provided similar regioselectivity, though toluene proved to be optimal, in which case catalyst loading could be reduced to 10 mol% while maintaining reasonable reaction times. Production of **3** was ultimately optimized using La(OTf)₃ to 91% isolated yield (91:3 regioselectivity), while **4** could be obtained with Zn(OTf)₂ in 76% yield (9:76 regioselectivity).

Bis-epoxide opening, and in particular, catalyst-controlled regioselectivity, proved to be quite general (Table 1). A variety of electron-rich and electron-deficient anilines produced either heterocyclic motif (entries 1 – 5), with La(OTf)₃ catalysis forming predominantly perhydroisoindoles **5** and Zn(OTf)₂ yielding perhydroisoquinolines **6**. In the case of the La(III)-promoted reactions, there was a direct correlation of the nucleophilicity of the aniline with the reaction rate, with electron-rich amines reacting faster. The rate of formation for perhydroisoquinoline **6** under Zn(II)-catalysis was largely unaffected by the electronics of the aniline, until a sufficiently electron deficient analogue (entry 5) was used. Thus, with *p*-trifluoromethylaniline, the reaction was significantly slower than with the more electron-rich anilines, which all proceeded at approximately the same rate. Heteroaryl amines including 2-aminopyridine and 2-aminothiazole failed to react using either La(OTf)₃ or Zn(OTf)₂, in which case fumagillol was fully recovered.

More basic amines were also well tolerated in the reaction (entries 7 – 9), with La(III) again proving to be optimal for perhydroisoindole formation. It was necessary, however, to increase the catalyst loading to 50 mol% in order to obtain reasonable reaction times, presumably due to the greater basicity of these amines leading to tighter interaction with the catalyst. An even greater reduction in reaction rate was observed with Zn(II) catalysis, rendering the reaction unacceptably slow (60 h, approx. 5–10% conversion). Use of Mg(OTf)₂ (50 mol%) as the catalyst, however, also led predominantly to the desired perhydroisoquinoline products (**6f** – **6g**) in acceptable reaction times (entries 7 – 9, 16 – 36 hrs). Addition of aromatic and aliphatic secondary amines were also carried out providing highly substituted tetrahydrofuran products **7** and **8**, both isolated as triflate salts (Table 1, entries 10 and 11).

Insights into the interaction of metal catalysts with fumagillol were achieved through a series of ¹³C NMR experiments (Figure 2, Supplementary Figure 6). In the ¹³C NMR spectra of fumagillol obtained with 2 mol% of paramagnetic catalysts Yb(OTf)₃ (*r* = 175 pm) or Fe(OTf)₂ (*r* = 140 pm),^{35,36} broadening of the C5 and C6 resonances was observed, indicating that different sized metals are preferentially bound to the pocket formed by the hydroxyl and methoxy groups of fumagillol (**7**). The same interaction was not observed in the C6-silylated analogue **10**, with only modest broadening of the C2, C1', and C2' signals observed.

To probe the importance of the interactions observed by ¹³C NMR, selectivity of silyl ether **11** under the optimized reaction conditions was evaluated. When **11** was reacted with several anilines, the regioselectivity obtained with La(III) catalysis inverted, leading predominantly to perhydroisoquinoline products as originally found in the Zn(II)-catalyzed reactions (Figure 2b). By comparison, reaction of **11** using Zn(II) became more selective to afford perhydroisoquinolines providing greater than 20:1 selectivity. These results suggest a

mechanism wherein coordination of the metal to the C6 hydroxyl group of fumagillol with different sized metals greatly affects the regiochemical outcome, either through multidentate ligand effects and/or conformational control.

The observed regioselectivity can be rationalized from a model of metal-coordinated amino alcohol intermediate **14**, obtained from opening of the more labile spirocyclic epoxide (Figure 2c).^{37,38} The larger La(III) catalyst may more easily accommodate the C6 hydroxyl group simultaneously with C1' epoxide activation (*cf.* **15**), thereby leading to tridentate coordination to the substrate wherein the amine is positioned closer and at a more optimal trajectory for addition to C1'. In contrast, smaller metals such as Zn(II) which cannot as easily accommodate the C6 hydroxyl while activating the second epoxide may adopt a looser bidentate coordination which places C2' closer the amine (*cf.* **16**). In the case of Zn(II) catalysis, activation of the second epoxide through adoption of **16** may be rate determining, as perhydroisoquinoline formation appeared to be largely independent of aniline nucleophilicity. Further studies to understand the precise mechanism leading to selectivity are currently underway.

The methodology was further extended by the use of L- and D-phenylalanine methyl esters which underwent lactonization after initial epoxide opening (Figure 3a). With Mg(OTf)₂ as catalyst, perhydroisoquinoline products **17** and **19**, respectively, were produced in approximately 3:1 regioselectivity relative to the perhydroisoindole- derived products (**18**, and **20/21**, respectively) for each amino acid. Further lactonization of the perhydroisoquinoline analogues was not observed. In comparison, the perhydroisoindole formed with D-phenylalanine (catalyzed by La(OTf)₃) lactonized *in situ* to afford the polycyclic morpholinone derivative **18**. Reaction with L-phenylalanine, however, formed isoindole **20** and morpholinone **21** in a 4:1 ratio. The observed resistance to lactonization of **21** can be rationalized from steric congestion caused by the additional pseudoaxial prenyl substituent at C2' which was calculated to be 3.1 kcal/mol higher in energy relative to diastereomer **18** (Supplementary Figure 7). Lactonization of **20** could eventually be accomplished under basic conditions to yield morpholinone **21** (85%).

Reaction of **1** with 2-ethynylaniline under Mg(OTf)₂ catalysis produced perhydroisoquinoline **22**, while La(III) afforded the expected perhydroisoindole product **23** (Figure 4a). Upon extended reaction times (48 h) with La(OTf)₃ or at elevated temperature (90 °C), the novel 4,1-benzoxazepine³⁹⁻⁴¹ **24** bearing a [4.2.1] ring system was formed from **23** in a highly efficient cascade process.⁴²⁻⁴⁵ Benzoxazepine **24** is presumably formed by initial hydroalkoxylation of the alkynyl alcohol of **23** to enol ether **25**^{46,47} followed by protonation to oxonium **26** (Figure 4b). Subsequent Prins cyclization⁴⁸ forms 4,1-benzoxazepine **24**, thereby providing a dramatic example of natural product remodeling *via* an unanticipated cascade sequence.

In summary, the natural product fumagillol has been selectively remodeled into a series of perhydroisoindoles and perhydroisoquinolines through sequential ring-opening with amines. Regiocontrol was achieved through choice of metal triflate catalysts, with smaller Zn(II) and Mg(II) catalysts leading to perhydroisoquinolines, while the larger La(III) catalyst favored production of perhydroisoindoles. Addition of secondary amines provided highly substituted

tetrahydrofurans. Perhydrosoindole products underwent further reactions, including lactonizations employing amino acid esters as epoxide-opening nucleophiles and bridged 4,1-benzoxazepines from an unexpected cascade sequence with 2-ethynylaniline. Remodeled structures produced in this study are currently being examined in a range of biological screens, including those as part of the Molecular Libraries Probe Production Centers Network (MLPCN, <http://mli.nih.gov/mli/>) and the NIMH Psychoactive Drug Screening Program (PDSP, <http://pdsp.med.unc.edu/indexR.html>). These studies should pave the way for work to remodel other natural product scaffolds to access novel chemotypes and pharmacological tools.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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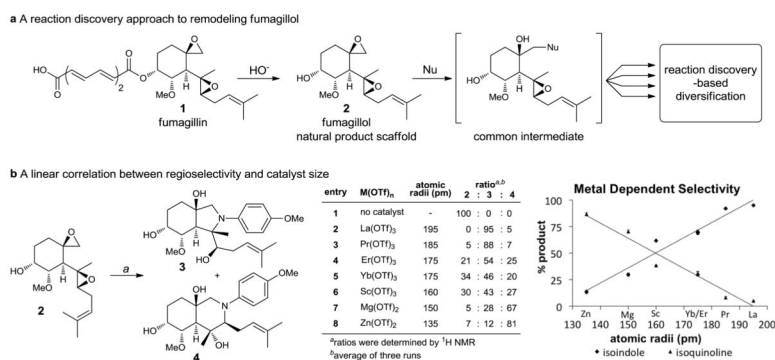


Figure 1. Natural Product Remodeling using Fumagillol

a, Fumagillol can be transformed into multiple chemotypes through a panel of related reaction conditions. Fumagillol was obtained by hydrolysis of crude fumagillin isolated from the fermentation broth of *Aspergillus fumigatus*. **b**, *a*) M(OTf)_n (10 mol%), *p*-anisidine (1.1 equiv.), DTBMP (60 mol%), toluene, 60 °C, 20 h; DTBMP = 2,6-*di-tert*-butyl-4-methylpyridine.

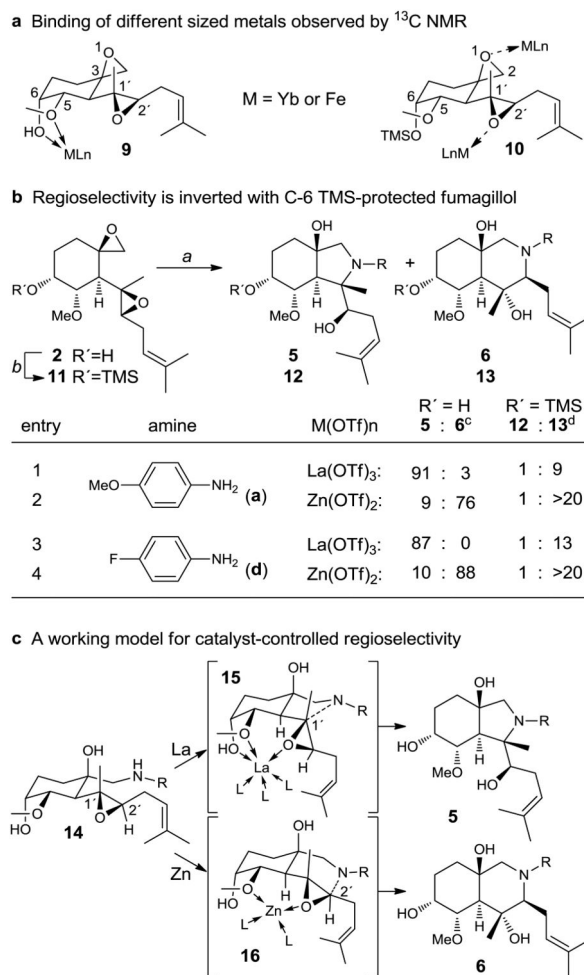
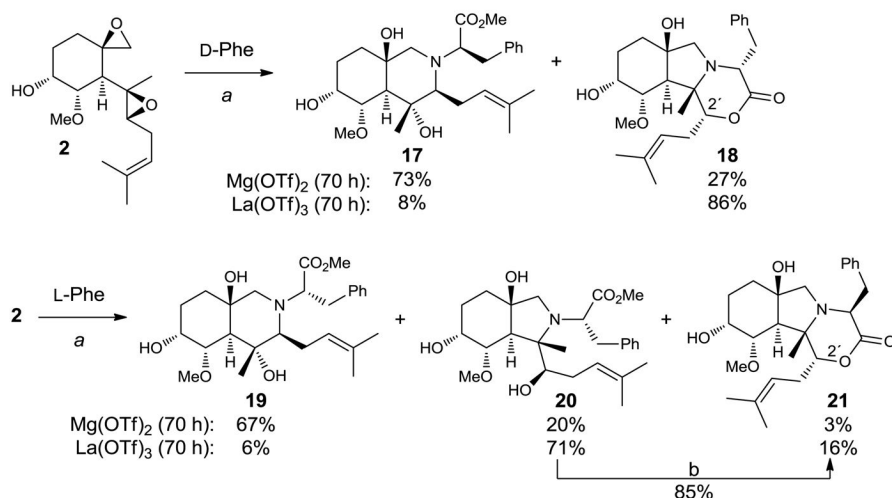


Figure 2. Mechanistic Studies

a, Metals of different sizes preferentially coordinate to the C-6 hydroxyl and C-5 methyl ether of fumagillol by ^{13}C NMR. **b**, Epoxide opening of TMS-protected fumagillol shows an inversion of regioselectivity; a) amine (1.1 equiv.), $M(\text{OTf})_n$ (10 mol%), DTBMP (60 mol %), toluene, 60 °C; b) TMSCl, imidazole, DMAP, CH_2Cl_2 , 83%; c) isolated yields; d) ratio by ^1H NMR. **c**, A working model demonstrating the role of the C-6 hydroxyl toward regioselectivity; DMAP = 4-dimethylaminopyridine, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TMS = trimethylsilyl.

a Phenylalanine as reaction partner.



b Molecular models of morpholinones **18** and **21**.

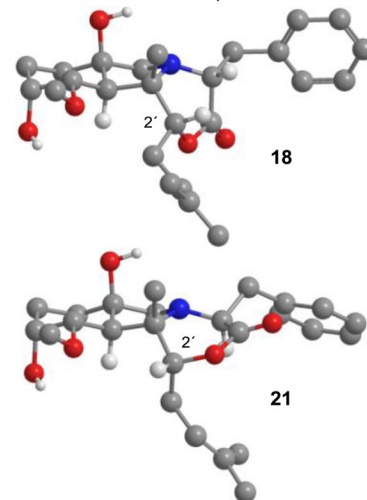


Figure 3. Use of amino acid esters as reaction partners

a, Selective formation of perhydroisoindoles, perhydroisoquinolines, or morpholinones with phenylalanine; a) amine (2.0 equiv.), M(OTf)_n (50 mol%), DTBMP (1.5 equiv.), toluene, 60 °C; b) NaOH (2.0 M), THF, rt, 6 h; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, Phe = phenylalanine. **b**, Molecular models of the phenylalanine-derived morpholinones **18** and **21**.

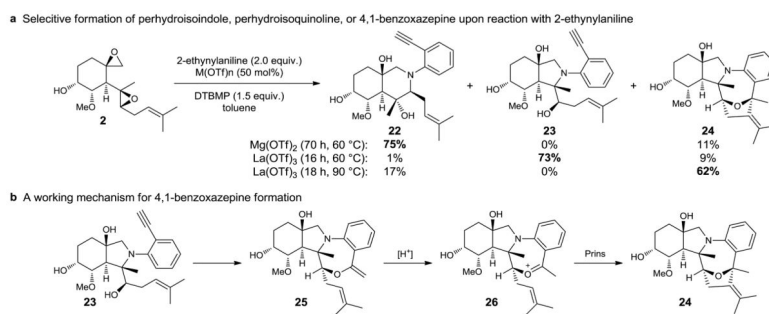
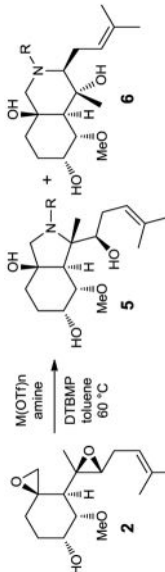
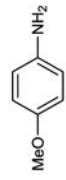
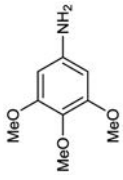
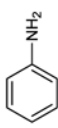
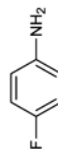

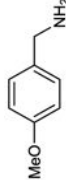


Figure 4. Reaction with 2-ethynylaniline
a, Selective formation of a perhydroisoindole, perhydroisoquinoline, or 4,1-benzoxazepine;
 DTBMP = 2,6-*di-tert*-butyl-4-methylpyridine. **b**, A novel cascade process to form a 4,1-
 benzoxazepine.

Table 1

Reaction with primary and secondary amines.



entry	amine	M(OTf) _n (rxn conditions)	reaction time	% yield	5: 6
1		La(OTf) ₃ ^a	7 h	91: 3	
		Zn(OTf) ₂ ^b	29 h	9: 76	
2		La(OTf) ₃ ^a	3 h	84: 0	
		Zn(OTf) ₂ ^b	24 h	6: 80	
3		La(OTf) ₃ ^a	29 h	89: 2	
		Zn(OTf) ₂ ^b	29 h	8: 65	
4		La(OTf) ₃ ^a	36 h	87: 0	
		Zn(OTf) ₂ ^b	29 h	10: 88	
5		La(OTf) ₃ ^a	4 d	40: 0	
		Zn(OTf) ₂ ^b	48 h	10: 61	
7		La(OTf) ₃ ^c	20 h	62: 25	
		Zn(OTf) ₂ ^b	60 h	0: 57	
		Mg(OTf) ₂ ^d	16 h	13: 82	

entry	amine	M(OTf) _n (rxn conditions)	reaction time	% yield
8		La(OTf) ₃ ^c	24 h	66: 32
		Zn(OTf) ₂ ^b	60 h	0: 2
		Mg(OTf) ₂ ^d	36 h	18: 74
9		La(OTf) ₃ ^c	20 h	49: 20
		Zn(OTf) ₂ ^b	60 h	0: 11
		Mg(OTf) ₂ ^d	20 h	12: 37
10		La(OTf) ₃ ^c		
		R = PMP		
		7 (74%)		
11		La(OTf) ₃ ^c		
		R = Bn		
		8 (75%)		

^a La(OTf)₃ (10 mol%), DTBMP (60 mol%), amine (1.1 equiv.);

^b Zn(OTf)₂ (10 mol%), DTBMP (60 mol%), amine (1.1 equiv.);

^c La(OTf)₃ (50 mol%), DTBMP (1.5 equiv.), amine (2.0 equiv.);

^d Mg(OTf)₂ (50 mol%), DTBMP (1.5 equiv.), amine (2.0 equiv.); DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, PMP = *p*-methoxyaniline.