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Taming of a Superbase for Selective Phenol Desilylation and Natural Product Isolation

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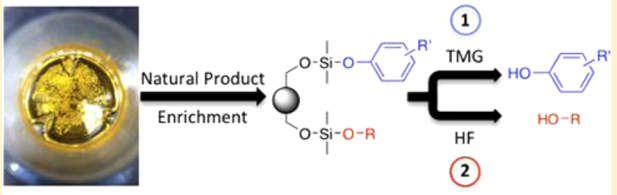
Supporting Information

ABSTRACT: Hydroxyl moieties are highly prevalent in natural products. We previously reported a chemoselective strategy for enrichment of hydroxyl-functionalized molecules by formation of a silyl ether bond to a resin. To generate smaller pools of molecules for analysis, we developed cleavage conditions to promote stepwise release of phenolic silyl ethers followed by aliphatic silyl ethers with a "tamed" version of the superbase 1,1,3,3−tetramethylguanadine. We demonstrate this as a general strategy for selective deprotection of phenolic silyl ethers under neutral conditions at room temperature.



The discovery, isolation, and synthesis of natural products are difficult endeavors. However, these molecules have been important to the scientific community for decades serving as drug candidates, inspiration for new biologically active scaffolds and prominent targets for synthetic chemists.[1,2] With the recent decline of molecules in the pharmaceutical pipeline, a resurgence of innovation is needed to enable both natural product synthesis and discovery.

Typically, biologically active molecules are discovered by screening of compound libraries generated either by combinatorial chemistry or from natural product extract materials. To date, only one molecule produced *de novo* by combinatorial methods has been introduced into the clinic.[1] Conversely, natural products and their scaffolds account for nearly half of the drugs currently on the market, with particular success in antibiotic and anticancer therapeutic development.[1,3] Despite this fact, natural product discovery efforts have declined in the last several decades because of the technical difficulties associated with isolation and characterization of minute quantities of material, and the synthesis and manipulation of complex molecular scaffolds.[4] New methods that facilitate compound isolation and detection of lower abundant molecules would therefore be beneficial.

We previously developed chemoselective isolation strategies to enable enrichment of subsets of molecules from complex mixtures including the hydroxyl moiety[5] and the carboxylic acid group.[6] Unlike traditional discovery methods that separate molecules by their physicochemical properties such as size or solubility, our method facilitates separation of molecules based upon their functional group composition (Figure 1).[7] The devised reagents are polystyrene-based resin beads appended with a chemoselective reactive group that captures only molecules that contain the targeted functionality, which remain affixed to the resin, while all others are washed away. The enriched subpool is subsequently released from the resin

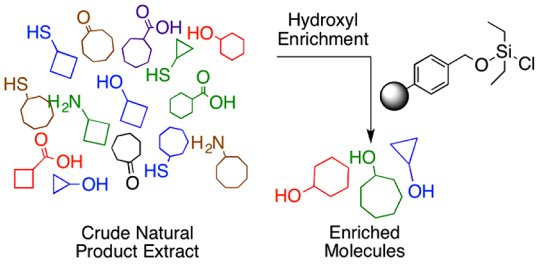


Figure 1. Chemoselective strategy for hydroxyl-containing natural product isolation.

yielding two distinct collections of molecules for biological testing.

In comparison to synthetic drugs, natural products contain a larger number of stereocenters, fewer nitrogen and sulfur atoms, and more oxygen atoms, which are present in several functional groups including ethers, ketones, carboxylic acids and hydroxyls. While the carboxylic acid moiety is found in only ∼15% of natural products, providing a small group of compounds following enrichment, the hydroxyl is present in approximately 70% of all natural products.[8] Accordingly, we aimed to develop an enrichment strategy capable of differentiating between aromatic and aliphatic alcohols, thus yielding two smaller subsets of molecules. Separation of phenols from the remaining aliphatic hydroxyl pool would be advantageous because this functional group is prevalent in drugs[9] and compounds containing these moieties possess antioxidant, antitumor, and antibacterial properties.[10,11] Routine pH-mediated extraction techniques do not enable the separation of all phenols from aliphatic and carboxylic acid-containing

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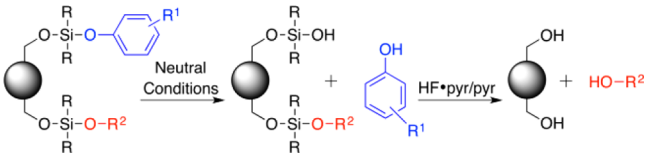
compounds because the pK_a values of these compounds span a wide range (Figure S1).[12] In addition, use of anion exchange resins promotes simultaneous isolation of phenols and carboxylic acids.[13]

We sought to tailor our previously developed enrichment strategy to achieve differentiation between aliphatic and aryl hydroxyl groups by taking advantage of the disparity in the pK_a values of phenolic (pK_a ~10) and aliphatic hydroxyl moieties (pK_a ~16). Attempts to promote selective capture by alteration of the base utilized during the coupling step were unsuccessful (data not shown). Instead, we turned our attention to the development of conditions under which both the aryl and aliphatic alcohols were captured, but selective cleavage of one molecule subpool could be achieved. Given the structural complexity and diversity present in natural product extract materials, we wished to generate mild conditions (i.e., neutral pH) to effect cleavage to minimize compound modification or degradation. Methods for the selective removal of aliphatic silyl ethers in the presence of aryl silyl ethers have been reported, but usually require the use of acidic reagents.[14,15] Selective cleavage of aryl silicon protecting groups[14,15] is most often accomplished under basic conditions[16−20] or with fluoride sources.[21,22] These deprotection methods are harsh, often resulting in hydrolysis, or display substrate dependent selectivity making them nonideal for our general isolation method. We hypothesized, however, that the lower pK_a value of the phenols might enable us to cleave these compounds at pH values near 7 (Scheme 1). Aliphatic hydroxyls would be retained on the resin and later released using previously reported conditions (HF•pyr/pyr).[5]

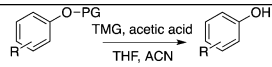
Scheme 1. Selective Release of Phenolic (Blue) Subpool to Enable Separation of These Compounds from Aliphatic Hydroxyl-Containing Molecules (Red), Which Are Removed in a Subsequent Cleavage Step

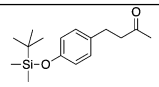
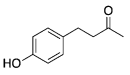
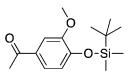
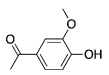
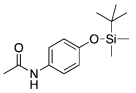
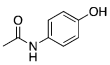
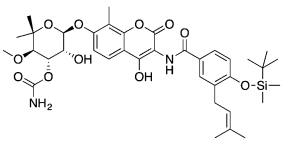
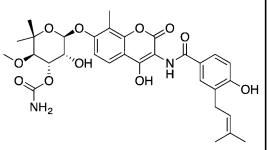


With the development of a neutral strategy in mind, we surveyed reported conditions to achieve selective cleavage of aryl silicon protecting groups. Use of 1,1,3,3-tetramethylguanadine (TMG), a catalyst utilized for a number of transformations,[23−25] caught our attention as this reagent enabled deprotection of a variety of phenolic substrates and showed good functional group tolerance.[26] Cleavage with this reagent was most effective in polar aprotic solvents (acetonitrile [ACN] gave best results) and at 50 °C. Neither of these conditions was well suited for use with polystyrene resin (does not swell in ACN) or natural product extract material (heat is avoided to protect structural integrity). Most concerning, however, was the fact that TMG is a superbase in ACN[27] and these cleavage reactions were performed at pH of ≥14. However, we saw an opportunity to "tame" the reactivity of this reagent. TMG has been proposed to facilitate selective aryl hydroxyl cleavage by a nucleophilic mechanism.[26] We reasoned that the basicity of TMG could be potentiated without significant loss of this nucleophilic character by protonation of the tertiary amines.

The previously reported selective TMG-promoted phenol deprotection was performed on *tert*-butyldimethylsilyl (TBDMS) functionalized compounds.[26] To discern if a potentiated TMG system could facilitate selective deprotection, we first examined substrates containing this protecting group in solution. We synthesized eight TBDMS protected molecules, four protected on a phenol and four on an aliphatic hydroxyl (Table 1 and Table S2). We selected glacial acetic acid for

Table 1. Deprotection of Phenols with Developed TMG Method



Substrate	Product	Yield
 1	 5	95% 75%[a]
 2	 6	63% 75%[a]
 3	 7	63% 78%[a]
 4	 8	58%

[a]The yield from the TIPS derivative of the corresponding substrate.

TMG protonation and determined that premixing of TMG in ACN/tetrahydrofuran with 1.15 equiv of acetic acid relative to the TMG lead to the best phenol deprotection yields.

Importantly, the pH of this cleavage cocktail is 7.5. Modest to good yields were observed with 10 equiv of TMG/acetic acid allowed to stir for 12 h at room temperature (Table 1 and Table S3). Even a complex scaffold such as novobiocin (**4**) was readily deprotected. The tri-isopropylsilyl (TIPS) aryl ethers of several substrates were also generated and found to cleave with the devised conditions (Table 1). TIPS and TBMDS protected aliphatic hydroxyl substrates were stable to these reaction conditions (Table S3 and Figures S64−S70). Thus, we successfully generated cleavage conditions that afford selective deprotection of trialkylarylsilyl ethers with retention of trialkylaliphatic silyl ethers. We expect these mild conditions will find application in synthetic efforts. In a complex total synthesis, trialkylsilicon groups are often not applied late in the synthetic scheme for protection of aryl hydroxyl groups because their unmasking usually requires extreme pH or a fluoride anion. Several well-known natural products, such as tetracycline,[28] vancomycin,[29] and novobiocin,[30] contain both aliphatic and aryl hydroxyl groups and their syntheses could benefit from the mild conditions described here.

Next, we sought to determine if this cleavage strategy could be utilized to promote natural product enrichment. Our previous work demonstrated that chemoselective capture of hydroxyl-containing compounds required use of a dialkylsiloxyl chloride-functionalized resin (**9** and **10**).[5] Given the steric and electronic differences between hydroxyl groups conjugated to

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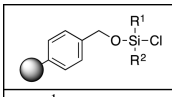
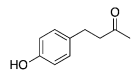
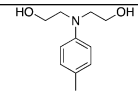
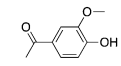
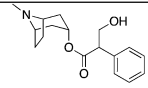
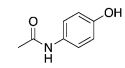
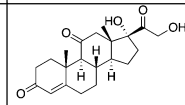
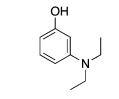
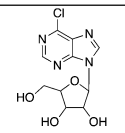
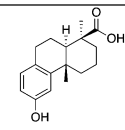
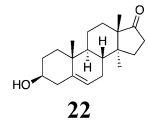
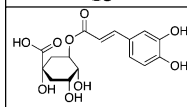
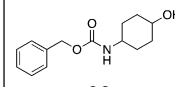
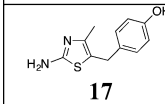
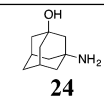
resin and TBDMS or TIPS ethers in solution, we expected that direct translation of the above-described deprotection conditions may not be possible. Accordingly, we examined an array of resin derivatives with varying alkyl substitutions about the silicon to determine which scaffold showed promise for generation of conditions under which aryl and aliphatic alcohols could be cleaved stepwise (Table 2, **9**–**13** and **S11**–**S15**). A mixture of four phenols and three aliphatic hydroxyls was coupled to the resin using previously devised conditions (Et_3N, dichloromethane/THF).[5] Next, cleavage was performed with TMG/acetic acid (20 equiv, 15 min, 30 °C) followed by HF•pyr/pyr to remove all remaining molecules. Ideally, only the phenols would be recovered following treatment with TMG and only aliphatic hydroxyl-containing molecules would be obtained from the HF cleavage. If ≥10% of the unintended group was seen in either cleavage, this was considered a chemoselective violation (e.g., an aliphatic hydroxyl compound was recovered during TMG cleavage).

Table 2. Examination of Polystyrene-Based Dialkylsiloxane Resins for Selective Release of Phenols with TMG and Cleavage of Aliphatic Hydroxyl Molecules with HF

	Avg. Phenol Recovery	Avg. Aliphatic Recovery	TMG Cleavage Violations	HF Cleavage Violations
R^1= methyl, R^2= methyl (**9**)	58%	52%	7	0
R^1= ethyl, R^2= ethyl (**10**)	48%	58%	2	2
R^1= methyl, R^2= ethyl (**11**)	45%	62%	3	4
R^1= methyl, R^2= isopropyl (**12**)	28%	54%	2	5
R^1= methyl, R^2= *t*-butyl (**13**)	9%	17%	2	1

The less bulky capture reagents gave better yields of both aryl and aliphatic hydroxyl groups (**9**–**11** versus **12** and **13**; Table 2 and Table S4). All examined resins displayed chemoselective violations, however, the dimethyl derivative (**9**) showed unintended cleavage of only the aliphatic hydroxyl groups with TMG while all other resins displayed unwanted cleavage of both hydroxyl group types (**10**–**13** and **S11**–**S15**). Given the comparatively good yields seen with **9** and the need to avoid only one type of unintended reaction with this scaffold, we focused attention on this resin. We discerned that use of 10 equiv of TMG/acetic acid for 10 min at room temperature gave the desired result (Table 3 and Table S5). A total of 28 compounds were coupled and released from resin, 13 phenols and 15 aliphatic alcohols. We obtained an average recovery yield of 62% for phenols, including the isolation of sterically hindered phenols and phenol-containing natural products (**6**, **15**, **16**, **S24**, **S25**; Figure S1). Aliphatic alcohols remained attached to resin through the TMG/acetic acid cleavage and were released upon exposure to HF•pyr/pyr. Primary (**18**–**21**, **S16**–**S19**), secondary (**22**, **23**, **S29**–**S22**), and tertiary (**24**, **S23**) alcohols were all readily enriched with an overall average recovery yield of 70% including atropine (**19**), an ester-containing natural product which was stable to the TMG and HF cleavage conditions (Table 3, Table S5, Figure S1). Finally, resin **9** was exposed to a set of compounds containing

Table 3. TMG and HF Recovery Yields for Model Aryl and Aliphatic Compounds

Substrate	TMG Yield	HF Yield	Substrate	TMG Yield	HF Yield
 **5**	94%	2%	 **18**	5%	68%
 **6**	71%	1%	 **19**	1%	74%
 **7**	86%	1%	 **20**	4%	81%
 **14**	77%	3%	 **21**	3%	50%
 **15**	70%	3%	 **22**	4%	85%
 **16**	50%	3%	 **23**	2%	84%
 **17**	52%	1%	 **24**	3%	59%

To demonstrate the utility of the devised strategy for enrichment of an endogenously produced phenolic compound, we turned our attention to streptonigrin (**25**), an aminoquinone that possesses antibiotic and antitumor properties. This natural product is produced by *Streptomyces flocculus* and has been the subject of considerable study because of its unique structural features (e.g., rotationally hindered biaryl linkages).[31,32] Crude extract[33] was subjected to enrichment resin **9**. Aryl hydroxyls were cleaved with TMG/acetic acid followed by the aliphatic hydroxyl group-containing compounds. The total ion chromatograms (TIC) for crude material (**a**) and phenol-containing compounds (**b**) are depicted in Figure 2. The TICs for the HF•pyr cleaved pool and the uncaptured molecules are in Figure S2.

Fewer compounds are present after separation of the phenols, enabling better resolution of the remaining components. Additionally, some features such as streptonigrin (red) represent a greater proportion of the aryl hydroxyl fraction than of the crude extract demonstrating enrichment. Importantly, 75% of the streptonigrin produced was recovered in the aryl alcohol fraction and only a minor quantity of this compound was found in the aliphatic pool confirming cleavage selectivity (8% yield; Figure S2). We quantified the extent of alcohol enrichment in comparison to compounds containing functional groups other than the hydroxyl to ensure that these molecules were not enriched, establishing the chemoselectivity of this method (Table S6, Figure S1).

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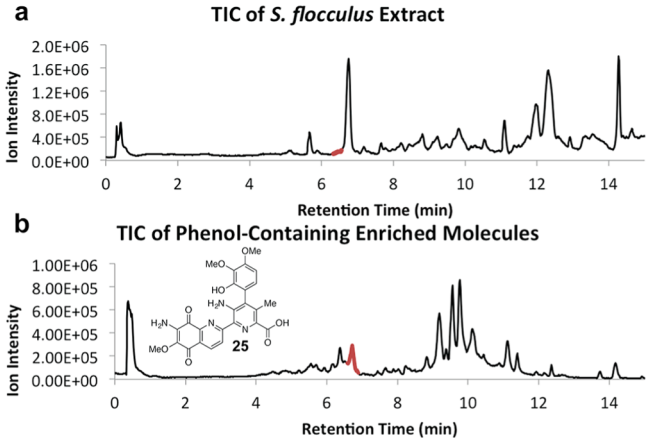

Figure 2. Total ion chromatograms for the enrichment of streptonigrin. (a) Crude *S. flocculus* extract with streptonigrin highlighted (red; ~6.6 min). (b) Following phenol enrichment, streptonigrin is the major species at this time point (Figure S3).

other functional groups that were spiked into the *S. flocculus* media. Phenols were enriched by an average of ~180-fold and aliphatic hydroxyl-containing molecules by an average of ~207-fold over other functional groups (Table S7) demonstrating the utility of the devised strategy to enrich compounds and promote the detection of species of low abundance.

We have developed the first selective strategy to facilitate cleavage of trialkylsilyl groups from aryl hydroxyls at neutral pH and room temperature, while aliphatic alcohols remain protected. The devised method was employed in the generation of a reversible enrichment tagging approach capable of separating aryl and aliphatic alcohols by stepwise release of these two classes of compounds. We expect that the reported strategy for the separation of aryl and aliphatic hydroxyl-containing compounds will find utility in many applications, including the discovery of natural products.

EXPERIMENTAL SECTION

General Materials and Methods. Triethylamine was distilled over barium oxide. Resin coupling reactions performed in biospin fritted vessels from Biorad under argon. Resin enrichment yields determined on a LC-MS-TOF equipped with a C18 column (1.8 μm, 2.1 × 50 mm). All sample and standard curve analysis was performed with the following gradient (A: 95% H_2O:5% ACN:0.5% Ammonium Acetate; B: 95% ACN:5% H_2O:0.5% Ammonium Acetate): 0−1 min 100% A at 0.5 mL/min, 1−5.5 min is composed of a linear gradient of 0−100% B also with a linear gradient flow rate change from 0.5 mL/min to 0.75 mL/min, 5.5−7 min at 0.75 mL/min is 100% B. The system was then allowed to equilibrate for 2 min back to 100% A. MS fragmentation voltages ranged from 75 to 200 V. NMR chemical shifts were reported relative to residual solvent peaks in parts per million. Infrared (IR) spectra were recorded using a FT-IR as a KBr pellet. Preparatory HPLC was performed on a C18 column (21.2 mm × 25 cm) with the following gradient: A: 100% H_2O, B: 100% ACN; 0−1 min 95% A: 5% B, 60 mL/min; 1−6 min linear gradient of 5% B to 95% B linear flow rate increase from 60 mL/min to 70 mL/min; 6−10 min hold at 95% B at 70 mL/min. Determination of protecting group retention on aliphatic hydroxyls was performed by analytical HPLC (C18, 4.6 × 150 mm, 5 μm) with the following gradient: A: 100% H_2O, B: 100% ACN; 0−1 min 5% B with a flow rate of 3 mL/min, 1−10 linear gradient from 5% to 95% B with an increase in flow rate from 3 mL/min to 4 mL/min, 10−15 min 95% B at 4 mL/min. Both HPLC methods were monitored at 254 and 280 nm.

Solution Phase Hydroxyl Protection. To a 20 mL scintillation vial was added 250 or 500 mg (1 equiv) of a model aliphatic or phenol compound, which was dissolved in 3 mL of either THF or DMF, depending on solubility. Next, 2 equiv of the chlorotrialkylsilane was added, followed by 4 equiv of imidazole. This solution was stirred overnight at room temperature. The reaction was quenched with water (5 mL) and extracted three times with ethyl acetate (10 mL). The organic extracts were combined, dried with sodium sulfate, filtered, and concentrated to dryness. The silylated compounds were purified by preparatory HPLC.

*TBDMS-4-(4-hydroxyphenyl)-2-butanone (**1**).* Clear, colorless oil; yield = 66%, 110 mg; ^{1}H NMR (C_4D_8O, 300 MHz): δ = 7.03 (d, J = 7.4 Hz, 2H), 6.73 (d, J = 7.3, 2H), 2.80−2.62 (m, 4H), 2.02 (s, 3H), 0.99 (s, 9H), 0.17 (3, 6H); ^{13}C NMR (C_4D_8O, 75 MHz): δ = 206.1, 154.6, 135.2, 129.9, 120.5, 45.6, 29.7, 29.6, 24.8, 18.8, −4.2; HRESIMS m/z $[M + NH_4]^+$ 296.2072 (calcd for $C_{16}H_{30}NO_2Si$, 296.2040).

*TBDMS-Acetovanillone (**2**).* Cream colored oil; yield = 95%, 164 mg; ^{1}H NMR (C_4D_8O, 300 MHz): δ = 7.54 (s, 1H), 7.50 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 3.84 (s, 3H), 2.47 (s, 3H), 1.01 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (C_4D_8O, 75 MHz): δ = 195.5, 151.8, 150.3, 132.7, 123.3, 120.9, 111.9, 55.6, 24.8, 19.1, −4.3; HRESIMS m/z $[M + H]^+$ 281.1599 (calcd for $C_{15}H_{25}O_3Si$, 281.1567).

*TBDMS-Acetaminophen (**3**).* Clear, colorless oil; yield = 88%, 186 mg; ^{1}H NMR (C_4D_8O, 300 MHz): δ = 9.07 (s, 1H), 7.46 (d, J = 7.7 Hz, 2H), 6.72 (d, J = 7.7 Hz, 2H), 1.99 (s, 3H), 0.98 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (C_4D_8O, 75 MHz): δ = 168.1, 152.0, 134.7, 121.1, 120.4, 24.7, 23.9, 18.8, −4.3; HRESIMS m/z $[M + H]^+$ 266.1591 (calcd for $C_{14}H_{24}NO_2Si$, 266.1571).

*TBDMS-Novobiocin (**4**).* Clear, colorless oil; yield = 90%, 131 mg; ^{1}H NMR (C_4D_8O, 400 MHz): δ = 8.85 (s, 1H), 7.50 (s, 1H), 7.46 (d, J = 7.9 Hz, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 6.59 (s, 1H), 5.60 (bs, 2H), 5.52 (s, 1H), 5.24 (d, J = 2.1 Hz, 1H), 5.03 (t, J = 7.1 Hz, 1H), 4.97 (dd, J = 7.9, 3.0 Hz, 1H), 4.34 (bs, 1H), 3.92 (s, 1H), 3.20 (s, 3H), 3.09 (d, J = 7.0 Hz, 2H), 2.21 (bs, 1H), 1.99 (s, 3H), 1.88 (s, 1H), 1.46 (s, 2H), 1.42 (s, 6H), 0.80 (s, 3H), 0.74 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (C_4D_8O, 100 MHz): δ = 168.2, 161.3, 158.5, 157.0, 138.1, 133.9, 133.7, 130.6, 127.9, 125.9, 125.6, 122.8, 122.7, 119.2, 114.4, 111.2, 103.9, 100.1, 82.2, 79.3, 72.5, 70.5, 61.4, 35.1, 30.7, 29.4, 29.1, 26.1, 24.9, 23.1, 21.4, 19.0, 18.0, 8.6, −4.0; HRESIMS m/z $[M + H]^+$ 727.3252 (calcd for $C_{37}H_{51}N_2O_{11}Si$, 727.3257).

*TIPS-4-(4-Hydroxyphenyl)-2-butanone (**TIPS-1, S1**).* Clear, colorless oil; yield = 75%, 358 mg; ^{1}H NMR (C_4D_8O, 300 MHz): δ = 7.02 (d, J = 7.5 Hz, 2H), 6.77 (d, J = 7.5 Hz, 2H), 2.81−2.60 (m, 4H), 2.02 (s, 3H), 1.34−1.17 (m, 3H), 1.19−1.0 (m, 9H); ^{13}C NMR (C_4D_8O, 75 MHz): δ = 206.2, 155.0, 135.0, 129.9, 120.3, 45.6, 18.3, 13.5; HRESIMS m/z $[M + NH_4]^+$ 338.2522 (calcd for $C_{19}H_{36}NO_2Si$, 338.2510).

*TIPS-Acetovanillone (**TIPS-2, S2**).* Cream colored oil; yield = 86%, 415 mg; ^{1}H NMR (C_4D_8O, 300 MHz): δ = 7.53 (s, 2H), 7.49 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 3.84 (s, 3H), 2.47 (s, 3H), 1.37−1.21 (m, 3H), 1.19−1.01 (m, 18H); ^{13}C NMR (C_4D_8O, 75 MHz): δ = 195.5, 151.7, 150.8, 132.4, 123.3, 120.4, 111.8, 55.5, 26.0, 18.3, 13.9; HRESIMS m/z $[M + H]^+$ 323.2043 (calcd for $C_{18}H_{31}O_3Si$, 323.2037).

*TIPS-Acetaminophen (**TIPS-3, S3**).* Clear, colorless oil; yield = 46%, 241 mg; ^{1}H NMR (C_4D_8O, 400 MHz): δ = 8.98 (bs, 1H), 7.47 (d, J = 7.9 Hz, 2H), 6.76 (d, J = 7.9 Hz, 2H), 1.99 (s, 3H), 1.34−1.18 (m, 3H), 1.18−1.01 (m, 18H); ^{13}C NMR (C_4D_8O, 100 MHz): δ = 167.9, 152.3, 134.6, 120.9, 120.2, 23.9, 18.3, 13.5; HRESIMS m/z $[M + H]^+$ 308.2052 (calcd for $C_{17}H_{30}NO_2Si$, 308.2040).

*TBDMS-2-N-Ethyl-anilino-ethanol (**S4**).* ^{1}H NMR (C_4D_8O, 500 MHz): δ = 7.18−7.05 (m, 2H), 6.67 (d, J = 7.5 Hz, 2H), 6.55 (t, J = 7.2 Hz, 1H), 3.77 (t, J = 6.4 Hz, 2H), 3.49−3.19 (m, 2H), 1.14 (t, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.12−0.01 (m, 6H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 148.8, 129.8, 116.3, 112.6, 61.6, 53.3, 46.1, 26.3, 18.9, 12.6, −5.2; HRESIMS m/z $[M + H]^+$ 280.2100 (calcd for $C_{16}H_{30}NOSi$, 280.2091).

*TIPS-2-N-Ethyl-anilino-ethanol (**S5**).* ^{1}H NMR (C_4D_8O, 500 MHz): δ = 7.10 (dd, J = 7.7, 7.3 Hz, 2H), 6.68 (d, J = 7.1 Hz, 2H), 6.54 (t, J = 7.2 Hz, 1H), 3.87 (t, J = 6.4 Hz, 2H), 3.49−3.31 (m, 4H), 1.17−1.06 (m, 24H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 148.8,

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129.7, 116.3, 112.5, 62.1, 53.4, 46.1, 18.4, 12.9, 12.5; HRESIMS m/z $[M + H]^+$ 322.2582 (calcd for $C_{19}H_{36}NOSi$, 322.2561).

*TBDMS-4-Z-Amino-cyclohexanol (**S6**).* ^1H NMR (C_4D_8O, 500 MHz): δ = 7.35−7.24 (m, 4H), 7.23 (t, J = 6.9 Hz, 1H), 6.26 (bs, 1H), 5.01 (s, 2H), 3.67−3.56 (m, 2H), 3.45−3.34 (m, 2H), 1.99−1.67 (m, 4H), 1.44−1.16 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 156.2, 138.7, 128.9, 128.3, 126.6, 71.3, 66.3, 50.0, 35.1, 31.4, 26.3, 26.2, 18.6, −4.4; HRESIMS m/z $[M + H]^+$ 364.2297 (calcd for $C_{20}H_{34}NO_3Si$, 364.2302).

*TIPS4-Z-Amino-cyclohexanol (**S7**).* ^1H NMR (C_4D_8O, 500 MHz): δ = 7.36−7.23 (m, 4H), 7.23 (t, J = 6.9, 1H), 6.25 (bs, 1H), 3.79 (s, 2H), 3.46−3.35 (m, 2H), 2.01−1.87 (m, 4H), 1.49−1.18 (m, 4H), 1.18−1.01 (m, 21H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 155.2, 138.8, 128.9, 128.7, 128.3, 71.5, 66.3, 50.1, 35.3, 31.5, 18.6, 13.3; HRESIMS m/z $[M + H]^+$ 406.2776 (calcd for $C_{23}H_{40}NO_3Si$, 406.2772).

*TBDMS-4-(Z-Amino)-1-butanol (**S8**).* ^1H NMR (C_4D_8O, 500 MHz): δ = 7.34−7.26 (m, 4H), 7.23 (t, J = 7.1 Hz, 1H), 6.34 (bs, 1H), 5.02 (s, 2H), 3.67−3.61 (m, 2H), 3.16−3.10 (m, 2H), 1.57−1.49 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 157.0, 138.8, 128.9, 128.6, 128.3, 66.3, 63.4, 41.4, 30.9, 27.4, 26.3, 18.8, −5.2; HRESIMS m/z $[M + H]^+$ 338.2177 (calcd for $C_{18}H_{32}NO_3Si$, 338.2146).

*TIPS-4-(Z-Amino)-1-butanol (**S9**).* ^1H NMR (C_4D_8O, 400 MHz): δ = 7.36−7.26 (m, 4H), 7.24 (t, J = 7.1 Hz, 1H), 6.37 (bs, 1H), 5.03 (s, 2H), 3.74 (t, J = 6.1 Hz, 2H), 3.15 (t, J = 6.0 Hz, 2H), 1.62−1.54 (m, 4H), 1.16−1.02 (m, 21H); ^{13}C NMR (C_4D_8O, 100 MHz): δ = 157.0, 138.7, 128.9, 128.5, 128.3, 66.3, 63.9, 41.5, 31.1, 27.4, 18.5, 18.4, 12.9; HRESIMS m/z $[M + H]^+$ 380.2626 (calcd for $C_{21}H_{38}NO_3Si$, 380.2615).

*TBDMS-erthryo-1,2-Diphenyl-ethanol (**S10**).* ^1H NMR (C_4D_8O, 500 MHz): δ = 7.28−7.11 (m, 10H), 6.93−6.87 (m, 2H), 6.45 (dd, J = 8.2, 7.5 Hz, 3H), 4.96 (d, J = 5.9 Hz, 1H), 4.79 (bd, J = 6.9 Hz, 1H), 4.50 (dd (apparent triplet, J = 6.4 Hz), 1H), 0.83 (d, J = 2.6 Hz, 9H), −0.13 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 148.3, 143.0, 141.5, 129.3, 128.5, 128.3, 128.2, 127.9, 127.6, 117.5, 114.2, 79.3, 65.5, 26.2, 18.7, −4.6, −5.1; HRESIMS m/z $[M + H]^+$ 404.2411 (calcd for $C_{26}H_{34}NOSi$, 404.2404).

TMG Deprotection of Aryl Hydroxyl Groups in Solution. To a one dram vial equipped with a stir bar was added 50 mg (1 equiv) of a TBDMS- or TIPS-protected aryl hydroxyl, which was then dissolved in 500 μL of THF. In a separate vial was mixed 500 μL of ACN, 10 equiv TMG, 11.5 equiv glacial acetic acid, and 10 μL H_2O. This cleavage cocktail was added to the protected hydroxyl and allowed to stir overnight at room temperature. The reaction was quenched with water (5 mL) and extracted three times with ethyl acetate (3 × 10 mL). The organic extracts were combined, dried with sodium sulfate, filtered, and concentrated to dryness. Purification was performed by silica gel chromatography with mixtures of ethyl acetate and hexanes or preparatory HPLC as described in General Methods section.

*Deprotection of **1** to Give 4-(4-Hydroxyphenyl)-2-butanone (**5**).* Yield = 95%, 16 mg; ^1H NMR (C_4D_8O, 400 MHz): δ = 6.94 (d, J = 7.4 Hz, 1H), 6.61 (d, J = 7.4 Hz, 1H), 2.75−2.60 (m, 4H), 2.01 (s, 3H); ^{13}C NMR (C_4D_8O, 100 MHz): δ = 206.3, 156.9, 132.7, 129.8, 115.9, 46.0, 29.8, 29.6; HRESIMS m/z $[M + NH_4]^+$ 182.1190 (calcd for $C_{10}H_{16}NO_2$, 182.1176).

*Deprotection of **2** to Give Acetovanillone (**6**).* Yield = 63%, 10 mg; ^1H NMR (C_4D_8O, 400 MHz): δ = 8.46 (bs, 1H), 7.40−7.37 (m, J = 2H), 6.68 (d, J = 7.1 Hz, 1H), 3.77 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (C_4D_8O, 100 MHz): δ = 195.3, 152.6, 148.4, 130.7, 124.2, 115.3, 111.1, 56.1, 25.9; HRESIMS m/z $[M + H]^+$ 167.0721 (calcd for $C_9H_{11}O_3$, 167.0703).

*Deprotection of **3** to Give Acetaminophen (**7**).* Yield = 63%, 10 mg; ^1H NMR (C_4D_8O, 500 MHz): δ = 8.74 (bs, 1H), 7.96 (bs, 1H), 7.36 (d, J = 7.8 Hz, 2H), 6.61 (d, J = 7.8 Hz, 2H), 1.96 (s, 3H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 167.6, 153.1, 131.1, 120.9, 115.0, 23.8; HRESIMS m/z $[M + H]^+$ 152.0711 (calcd for $C_8H_{10}NO_2$, 152.0706).

*Deprotection of **4** to Give Novobiocin (**8**).* Yield = 58%, 14 mg; ^1H NMR (C_4D_8O, 500 MHz): δ = 9.22 (bs, 1H), 9.08 (bs, 1H), 7.81−7.75 (m, 2H), 7.72 (d, J = 7.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 7.4 Hz, 1H), 5.93 (bs, 2H), 5.55 (s, 1H), 5.39 (t, J = 7.4 Hz, 1H), 5.29 (dd, J = 8.0, 3.0 Hz, 1H), 4.5 (s, 2H), 4.23 (s, 1H), 4.66 (d, J = 5.0, 1H), 3.67−3.47 (m, 6H), 3.37 (d, J = 7.3 Hz, 2H), 2.58 (s, 2H), 2.31 (s, 3H), 1.81−1.68 (m, 6H), 1.30 (s, 3H), 1.12 (s, 2H); ^{13}C NMR (C_4D_8O, 125 MHz): δ = 168.3, 161.3, 160.7, 158.4, 157.0, 150.9, 133.4, 130.5, 129.6, 128.1, 123.6, 122.9, 122.7, 115.4, 114.4, 111.2, 104.0, 100.1, 82.2, 79.3, 72.6, 70.5, 68.2, 61.5, 29.1, 28.9, 26.3, 23.2, 17.9, 8.7; HRESIMS m/z $[M + H]^+$ 613.2367 (calcd for $C_{31}H_{37}N_2O_{11}$, 613.2392).

*Deprotection of **TIPS-1** to Give 4-(4-Hydroxyphenyl)-2-butanone (**5**).* Yield = 75%, 19 mg; ^1H NMR (C_4D_8O, 400 MHz): δ = 7.96 (bs, 1H), 6.95 (d, J = 7.4 Hz, 2H), 6.61 (d, J = 7.4 Hz, 2H), 2.76−2.60 (m, 4H), 2.01 (s, 3H); ^{13}C NMR (C_4D_8O, 100 MHz): δ = 206.5, 156.9, 132.8, 129.9, 116.0, 46.0, 29.9, 29.7; HRESIMS m/z $[M + NH_4]^+$ 182.1182 (calcd for $C_{10}H_{16}NO_2$, 182.1176).

*Deprotection of **TIPS-2** to Give Acetovanillone (**6**).* Yield = 75%, 20 mg; ^1H NMR (C_4D_8O, 400 MHz): δ = (bs, 1H), 7.59−7.51 (m, 2H), 6.85 (d, J = 7.1 Hz, 1H), 3.94 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (C_4D_8O, 100 MHz): δ = 195.3, 152.6, 148.4, 130.6, 124.2, 115.3, 111.1, 56.1, 25.9; HRESIMS m/z $[M + H]^+$ 167.0702 (calcd for $C_9H_{11}O_3$, 167.0703).

*Deprotection of **TIPS-3** to Give Acetaminophen (**7**).* Reaction of 171 mg, Yield = 79%, 64 mg; ^1H NMR ($(CD_3)_2SO$, 500 MHz): δ = 9.63 (s, 1H), 9.13 (s, 1H), 7.33 (d, J = 6.8 Hz, 2H), 6.67 (d, J = 6.9 Hz, 2H), 1.97 (s, 3H); ^{13}C NMR ($(CD_3)_2SO$, 500 MHz): δ = 167.6, 153.2, 131.0, 120.9, 115.0, 23.7; HRESIMS m/z $[M + H]^+$ 152.0706 (calcd for $C_8H_{10}NO_2$, 152.0706).

Activation of Resin for Hydroxyl Group Capture. To a 20 mL scintillation vial equipped with a septum was added 200 mg of hydroxymethyl polystyrene resin (loading capacity of 1.1 mmol/g). The vessel was purged with Ar. The resin was swollen in 3 mL of anhydrous dichloromethane (DCM). To this was added 14 equiv of freshly distilled triethylamine (3.1 mmol, 450 μL) followed by 10 equiv of the desired dichlorodialkylsilane (2.2 mmol). Next, the resin was removed from Ar atmosphere, 1.2 equiv of 4-dimethylaminopyridine (DMAP, 0.26 mmol, 32 mg) was added, and the vessel was quickly capped. The resin was agitated for 4 h at room temperature. Next, the resin was filtered through a 10 mL biospin vessel under positive Ar pressure and rinsed 3 × 8 mL with anhydrous DCM. This resin was reswollen in 2.5 mL of anhydrous DCM and aliquoted into 5 oven-dried 2 mL vials. Three of the five vials were capped with a septum and placed under Ar. The fourth vial was transferred to a 2 mL biospin vessel and rinsed with 1:1 THF:MeOH. This hydrolyzes the Si−Cl bond to yield inactivated resin that will not capture hydroxyl-containing molecules to provide a control. The loading capacity for resin **9** was 0.2 mmol/g and was determined as previously described.[6] Coupling with activated resin **9** and washing of the resin prior to cleavage were performed as previously described.[6]

*Chlorodimethyl Benzylsiloxane Resin (**9**).* FT-IR (on-bead KBr pellet) ν_{max}: 2922, 1068, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.8, 2.4.

*Chlorodiethyl Benzylsiloxane Resin (**10**).[5] Chloroethylmethyl Benzylsiloxane Resin (**11**).* FT-IR (on-bead KBr pellet) ν_{max}: 3025, 2921, 1071, 757, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.8, 10.5, 6.5, 0.2.

*Chloroisopropylmethyl Benzylsiloxane Resin (**12**).* FT-IR (on-bead KBr pellet) ν_{max}: 3025, 2923, 1064, 757, 696 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.9, 20.8, 17.7, 16.6, 0.9.

*Chloro-t-butylmethyl Benzylsiloxane Resin (**13**).* FT-IR (on-bead KBr pellet) ν_{max}: 3025, 2924, 1076, 760, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.9, 25.5, 20.8, −2.5.

*Chloromethylphenyl Benzylsiloxane Resin (**S11**).* FT-IR (on-bead KBr pellet) ν_{max}: 3025, 2921, 2361, 1069, 758, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 133.9, 41.0, 1.4.

*Chloroisobutylmethyl Benzylsiloxane Resin (**S12**).* FT-IR (on-bead KBr pellet) ν_{max}: 3025, 2922, 1070, 757, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.9, 28.7, 26.1, 25.9, 24.4, 1.9.

*Chloro-n-butylmethyl Benzylsiloxane Resin (**S13**).* FT-IR (on-bead KBr pellet) ν_{max}: 3025, 2922, 1071, 758, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.8, 26.2, 25.1, 18.1, 13.9, 0.8.

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*Chlorocyclohexylmethyl Benzylsiloxane Resin (**S14**).* FT-IR (on-bead KBr pellet) ν_{max}: 3025, 2921, 1069, 758, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.9, 28.5, 28.1, 27.8, 27.0, 26.5, −1.2.

*Chlorodecylmethyl Benzylsiloxane Resin (**S15**).* FT-IR (on-bead KBr pellet) ν_{max}: 3024, 2922, 1069, 757, 698 cm^{-1}; gel-phase ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 40.8, 33.3, 32.4, 30.1, 29.8, 23.1, 18.4, 14.4, 1.3.

Cleavage of Phenols from Resin 9. Dried resin was transferred to a 2 mL eppendorf tube and swollen in 400 μL of THF. In a separate vial, 100 μL of ACN, 10 equiv of 1,1,3,3-tetramethylguanidine (TMG, 10 μL, 0.08 mmol), and 11.5 equiv of glacial acetic acid (5.5 μL, 0.09 mmol) were mixed. This cleavage solution was added to the resin and agitated for 10 min. The resin was filtered through a 1 mL biospin and rinsed with DCM, toluene, and THF. This solution was concentrated to dryness, redissolved in 2 mL of a 2/1/1 mixture of H_2O/THF/MeOH, and 1 μL was injected onto a LC-MS-TOF for quantification as previously described.[6]

Cleavage of Aliphatic Alcohols from Resin 9. The resin that had been previously subjected to TMG cleavage to liberate the phenols was reswollen in 500 μL of THF and transferred to a 2 mL eppendorf tube. To the resin was added 50 μL of pyridine and 50 μL of 70% HF/30% pyridine solution. After agitating for 3 h at room temperature, the solution was quenched with 500 μL of methoxytrimethylsilane to hydrolyze excess HF. The resin was washed in a 1 mL biospin with THF, DCM, and THF. This solution was concentrated to dryness, redissolved in 2 mL of a 2/1/1 mixture of H_2O/THF/MeOH, and 1 μL was injected onto a LC-MS-TOF for quantification as previously described.[6]

Procedure for the Preparation of *Streptomyces flocculus* Extract. *Streptomyces flocculus* was obtained from ATCC (13257) as a freeze−dried pellet. An initial seed culture of 5 mL was prepared (glucose 10 g/L, beef extract 4 g/L, gelysate peptone 4 g/L, yeast extract 1 g/L, NaCl 2.5 g/L) and grown at 29 °C for 72 h. This 5 mL culture was transferred to 120 mL of the described broth in a 250 mL baffled flask and shaken at 180 rpm at 28 °C for 72 h. For large scale streptonigrin production, 7.5 mL of the previous culture was added to 150 mL of the follow medium: 30 g/L glucose, 13 g/L potassium phosphate, 0.5 g/L $MgSO_4$-7 H_2O, 0.4 g/L $CaSO_4$−$2H_2O$, 0.01 g/L $FeSO_4$−$7H_2O$, 1.9 g/L NaCl, 0.9 g/L KCl, 0.5 g/L NH_4Cl, pH = 7.2. This 150 mL of culture was placed into a 500 mL baffled flask and shaken a 180 rpm at 28 °C for 5 days. NOTE: Autoclave salts and phosphates together and autoclave glucose by itself and then combine aseptically. After 5 days, the cultures were centrifuged at 7000 rpm for 30 min. The broth was collected and adjusted to a pH of 4 with 6 N HCl. The culture was extracted with hexanes (3 × 1 L) to remove hydrophobic molecules. The remaining broth was extracted with ethyl acetate (3 × 1 L) and concentrated to dryness to yield the crude biological extract.

Enrichment of Endogenously Produced Streptonigrin from *S. flocculus*. For this experiment, 75 mg of crude extract was used. It was assumed that 70% of the molecules in this crude extract contain at least one hydroxyl moiety.[8] Therefore, we calculated that we wanted to capture 52 mg of the total 75 mg sample. We also assumed an average molecular weight of all molecules in the extract to be 350 g/mol, which yields 0.15 mmol in 52 mg of crude sample. To ensure sufficient coupling of all molecules, we applied 2 equiv of the resin relative to the crude extract; therefore, we applied 0.3 mmol of resin **9** (loading capacity = 0.2 mmol/g) to the 75 mg of bacterial extract. To generate the capture reagent, 1.5 g of hydroxymethyl polystyrene (1.1 mmol/g, 1.65 mmol, 1 equiv relative to resin generation reagents) was added to a flame-dried 100 mL round-bottom flask and swollen in 20 mL of anhydrous DCM under Ar. Next was added 3.3 mL of Et_3N (23.1 mmol, 14 equiv), 2 mL of dichlorodimethylsilane (16.5 mmol, 10 equiv), and 222 mg of DMAP (1.8 mmol, 1.1 equiv). The flask was capped and agitated at room temperature for 4 h. The resin was transferred to a 20 mL biospin and rinsed under Ar with anhydrous DCM three times. The resin was reswollen in 30 mL of anhydrous DCM and transferred to a new flame-dried round-bottom flask under Ar. The crude extract was dissolved in 2 mL of anhydrous THF and added to the resin after 350 μL of Et_3N (2.4 mmol, 8 equiv). The flask was capped and allowed to agitate overnight at room temperature. The resin was then poured into a 20 mL biospin vessel and the drain was collected. The resin was rinsed with 10 mL of DCM followed by 10 mL of THF. The flow through was added to the initial drain. The resin was then subjected to the rest of the wash protocol described above to remove any noncovalently associated molecules. The resin vessel was capped and allowed to dry for 1 h at room temperature in a vacuum desiccator. Once dried, the resin was transferred to a 50 mL round-bottom flask and swollen in 10 mL of THF. In a separate vessel was mixed 5 mL of ACN, 384 μL of TMG (3.0 mmol, 10 equiv), and 207 μL of glacial acetic acid (3.5 mmol, 11.5 equiv). This mixture was added to the resin and agitated for 10 min. After this time, the resin was again transferred to a 20 mL biospin vessel and the drain collected. The resin was rinsed with DCM × 3, THF × 3, 1:1 DCM:MeOH, and THF × 3. All of these rinses were combined to yield those compounds that contained the phenol functionality, including our desired biological molecule, streptonigrin. Cleavage of the remaining aliphatic hydroxyl-containing molecules was performed by transferring the resin to a Nalgene vessel and swelling it in 20 mL of THF. Next was added 3.8 mL of HF/pyr (30 equiv) and 3.8 mL of pyridine (30 equiv). The mixture was agitated at room temperature for 3 h and then quenched with 20 mL of methoxytrimethylsilane (85 equiv). Then resin was filtered and rinsed with DCM × 3, THF × 3, 1:1 DCM:MeOH, and THF × 3. All of these rinses were combined and concentrated to yield a pool of molecules that contain aliphatic hydroxyl moieties.

Separation of Aliphatic Hydroxyls, Phenols, and Carboxylic Acids with Acid/Base Solution Phase Extraction. 100 mg of crude, dried *S. flocculus* extract was dissolved in 200 mL water. To this was added 0.0008 mmol each of 2 carboxylic acid-containing molecules, 6 phenol compounds, 2 amines, 1 carbonyl-containing molecule, and 6 aliphatic hydroxyl molecules. This solution was then basified to a pH of 10 with sodium bicarbonate. This solution was extracted 3 times with 200 mL of ethyl acetate. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated to dryness. The water layer was acidified with 2 N HCl to a pH of 2. This solution was extracted 3 times with 200 mL of ethyl acetate and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated to dryness. The dried organic extracts were dissolved in a mixture of 2:1:1 H_2O:THF:MeOH and 1 μL injections were made on a LC-MS-TOF. Analysis was performed to determine which molecules were extracted into which layer from the extraction. As shown in Supporting Information Table 1, separation of phenols, aliphatic hydroxyl-containing molecules, and carboxylic acids is not possible by acid/base extractions.

■ ASSOCIATED CONTENT

Supporting Information

Contains referenced Figures, Tables, additional procedures, ^1H and ^{13}C NMR spectra, and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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