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Application of the Solid-Supported Glaser–Hay Reaction to Natural Product Synthesis

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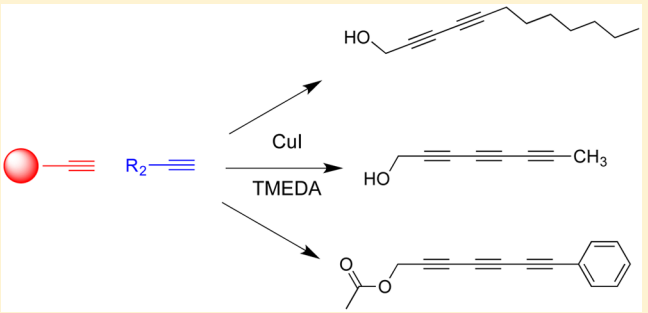
Supporting Information

ABSTRACT: The Glaser–Hay coupling of terminal alkynes is a useful synthetic reaction for the preparation of polyynes; however, chemoselectivity issues have precluded its widespread utilization. Conducting the reaction on a solid-support provides a mechanism to alleviate the chemoselectivity issues and provide products in high purities and yields. Moreover, the polyyne core is a key component to several natural products. Herein, we describe the application of a solid-supported Glaser–Hay reaction in the preparation of several natural products. These compounds were then screened for antibacterial activity, illustrating the utility of the methodology.



Polyyne core structures are prevalent in various natural products and consist of a series of conjugated acetylenic units.[1−3] Over 1,000 of these naturally occurring molecules have been isolated from organisms such as plants, fungi, and coral.[2] These structures exhibit numerous biological activities including antibacterial, antifungal, anti-HIV, and anticancer properties.[3−7] Therefore, synthetic routes to the preparation of these structures are necessary to further study their benefits and develop novel therapeutic analogs.

One approach to access these conjugated alkyne cores involves the Glaser–Hay reaction. This reaction involves the coupling of two terminal alkynes and was developed in the 1800s.[8] The reaction was later optimized to lower the temperature and increase the rate of the reaction; however, the lack of chemoselectivity precluded its use, as a mixture of three coupling products could be obtained when using two unique terminal alkyne reagents (Figure 1).[9,10] This has been synthetically addressed via the transition to the Cadiot–Chodkiewicz reaction between a halo-alkyne and a terminal alkyne to differentiate the reaction partners.[11,12] While this approach does proffer a degree of chemoselectivity, homocoupling is still observed and additional synthetic effort must be employed to prepare the halo-alkynes.[13−15] Based on the asymmetrical nature of many of these natural product derivatives, a more efficient mechanism to address chemoselectivity issues is required. Recently, we reported the solid-supported Glaser–Hay reaction as a mechanism to address several key pitfalls associated with the Glaser–Hay reaction (Figure 1).[16−18]

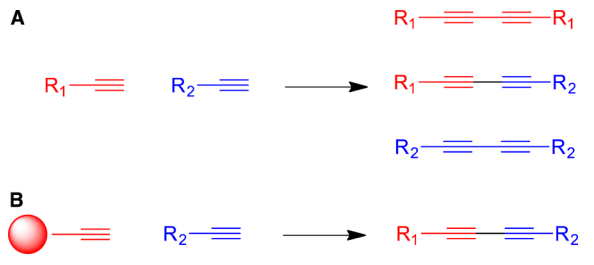


Figure 1. Glaser–Hay coupling of terminal alkynes. (A) Traditional Glaser–Hay reactions result in three diynes. (B) Solid-supported Glaser–Hay reaction yields only the heterodimeric product after resin cleavage.

The solid-supported Glaser–Hay coupling requires the immobilization of one terminal alkyne on a polystyrene resin. Subsequent reaction with another soluble alkyne affords the asymmetrical diyne in high yield and purity. Homodimerization of the immobilized alkyne is precluded by the pseudo-high dilution conditions of the solid support, and homodimerization of the soluble alkyne (used in excess) can simply be washed away from the solid support. Moreover, we developed a methodology to perform these solid-supported couplings with TMS-acetylene to sequentially add alkyne units, yielding highly conjugated asymmetrical polyynes.[16] Based on the success of this methodology, we became interested in employing the solid-supported Glaser–Hay reaction toward the synthesis of biologically relevant natural products. Herein, we report the application of the reaction to the preparation of four natural products and their subsequent screening for antibacterial activity.

Many corals have been found to be rich in natural products that contain antibacterial, antifungal, and cytotoxic properties. Specifically, numerous acetylenic polyynes have been isolated from the genus *Montipora*, a velvet coral.[19] The most directly accessible natural product that lends itself to this technology is

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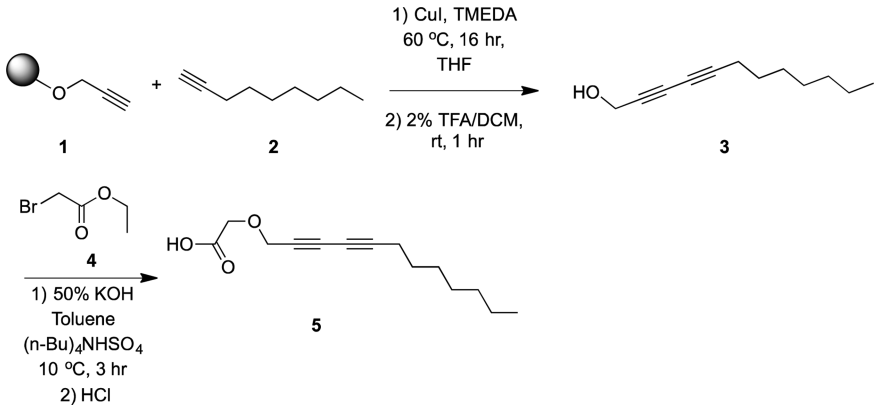
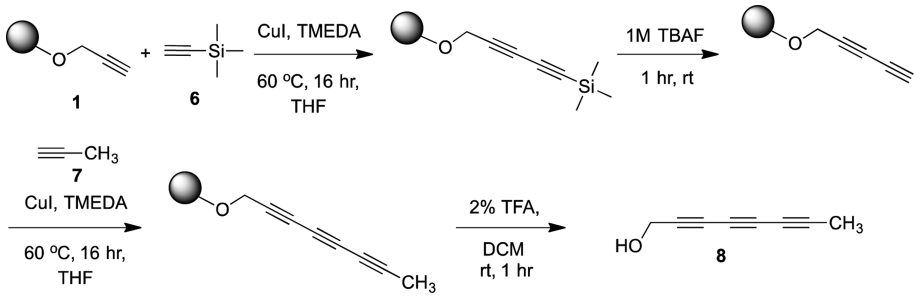
Scheme 1



Scheme 2



2,4-dodecadinyl alcohol (**3**), an asymmetrical diyne shown to exhibit cytotoxicity against human tumor lines.[2] Numerous research groups have described the synthesis of this natural product.[20−24] For example, Stefani et al. report this synthesis via a Cadiot−Chodkiewicz coupling with a reported yield of 76%.[24] However, this reported synthesis requires hazardous reagents and requires a preliminary synthetic step to synthesize a halogenated alkyne. Another synthesis reported by Fiandanese et al. requires numerous and sometimes harsh reagents, and six synthetic steps, and has a 42% yield.[23] Both syntheses also required tedious purification steps postreaction. We hypothesized that the solid-supported Glaser−Hay reaction would be optimal to obtain this product in fewer steps using milder conditions and afford higher yields.

Immobilization of propargyl alcohol on a trityl chloride polystyrene resin (**1**) at ∼0.7 mmol/g, as previously described,[17] facilitated the subsequent Glaser−Hay reaction with 1-nonyne (**2**) in the presence of a CuI/TMEDA catalyst system (Scheme 1). Following successive DCM/MeOH washes of the resin, **3** was cleaved from the resin using 2% TFA in DCM in 1 h. After a silica plug, **3** was obtained in a 75% yield in high purity after essentially a single synthetic step. Analysis via ^{1}H NMR, ^{13}C NMR, and GC/MS confirmed its identity and was in accordance with previously reported literature values.[23] Overall, utilizing the solid-supported Glaser−Hay methodology to synthesize this product eliminated harsh reagents, halogenated precursor compounds, and synthetic steps required in previously reported syntheses and produced the product in a better or comparable yield.

A derivative of **3**, Montiporic Acid A (**5**) is another common polyyne isolated from this velvet coral species.[2] Montiporic Acid A has been isolated from the eggs of this coral and was shown to possess significant cytotoxicity against P-338 murine leukemia cells. It has also been proven to be an efficient antibacterial agent against *E. coli*.[23] Conveniently, **5** can be accessed directly from **3** via an S_N2 reaction with 2-bromoacetate (**4**) followed by an ester hydrolysis (Scheme 1) as previously reported. Synthesis of **5** was achieved in good yield (49%) and analyzed via ^{1}H NMR, ^{13}C NMR, and GC/MS to confirm its purity and identity. Thus, our methodology allowed us to prepare **5** in three synthetic steps and in comparable yield to the previously reported synthesis that required six steps.

This methodology can also readily be employed toward triyne natural products. Toward this end, we initially targeted the preparation of octatriyn-1-ol (**8**), originally isolated from a fungus, *Kuehneromyces mutabilis*, in 1973.[25] This compound and similar derivatives were shown to possess antibacterial activities. Previous syntheses have utilized a Fritsch−Buttenberg−Wiechell rearrangement to prepare the triyne core.[26] Overall, this synthesis requires eight synthetic steps to generate **8**. This reported methodology also requires numerous reagents, including some that are hazardous, and careful reaction temperature control leading to an overall yield of only 3%.[26]

Building on our previously reported methodology for extending the acetylenic scaffold,[16] we developed a synthetic route toward octatriyn-1-ol (Scheme 2), decreasing the synthetic steps and number of reagents used from previous reports as well as increasing yield. Beginning with the previously described propargyl alcohol polystyrene resin (**1**), TMS-acetylene (**6**) was coupled using the Glaser−Hay conditions. The TMS group was then removed using a TBAF/DCM solution, regenerating the terminal alkyne. Propyne (**7**) was then coupled to the resin using the Glaser−Hay reaction and the product was cleaved with a 2% TFA solution, affording the desired asymmetrical triyne natural product, **8**. Following a silica plug purification, **8** was obtained in a 68% yield and analyzed by NMR and MS, which

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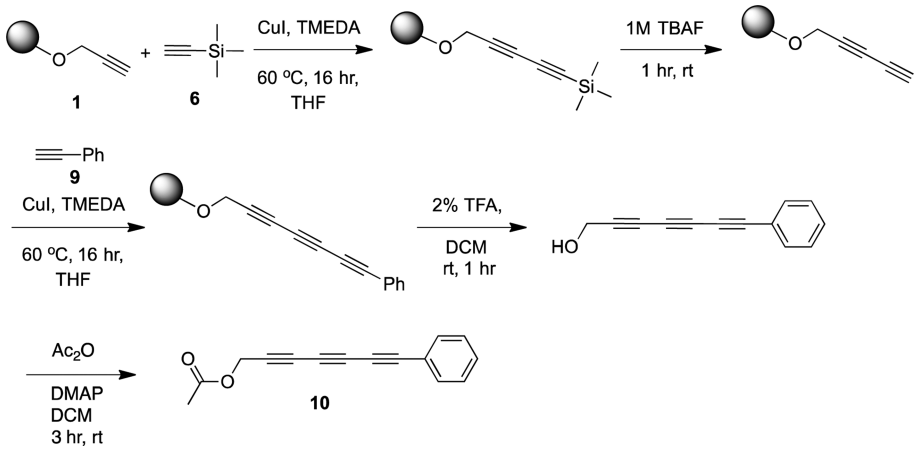
Scheme 3



corresponded to previously reported values. This is a dramatic increase over the current literature synthesis, which was performed with only a 3% overall yield and in an additional four steps.[26]

Finally, another triyne natural product is readily accessible using a similar methodology to the preparation of octariyn-1-ol. Phenylhepta-2,4,6-trinyl acetate (**10**) was originally isolated from several species of *Bidens* in the Aster family of plants and has shown antibacterial properties.[2] A previously reported synthesis was utilized starting from 1,4-butynediol, and following the addition of a TBDPS protecting group, it is reacted with a lithiated phenylacetylene and undergoes a Fritch−Butenberg−Wiechell rearrangement to produce the triyne core.[26] This synthetic strategy requires eight total steps and the use of harsh chemical conditions, affording **10** in a 14% yield. Utilizing our previously described solid-supported strategy the triyne core is readily accessible in minimal steps and can be further elaborated to generate the acetate (Scheme 3).

The previously described Glaser−Hay coupling with TMS followed by TBAF-induced TMS deprotection was employed to prepare the immobilized polyyne core, followed by the capping of the polyyne with phenylacetylene (**9**). The solid support was then cleaved to afford the triynol product. The alcohol was acetylated with acetic anhydride in the presence of DMAP to afford the desired product. Upon acetylation, the reaction was extracted and washed with DCM/H_2O and dried with $MgSO_4$. The triyne **10** was then purified on a silica column, affording the desired natural product in a 46% yield, a marked improvement. The product was then analyzed via NMR and MS and matched to previously reported spectra. Utilizing the solid supported Glaser−Hay methodology we were able to eliminate synthetic steps, as well as harsh and excessive reagents, and drastically improve the yield of this natural product.

With the natural products in hand, we wanted to quickly assess their antibacterial properties. Some have already been classified as antibacterial, while others exhibited other biological relevance, but all harbor a similar alkynyl core. Each of the products was dissolved in DMSO to generate stock solutions at 50 mg/mL. The compounds were then introduced in triplicate at various concentrations to *E. coli* cultures at different cellular densities to assess if the compounds either prevented bacterial growth (assay at low density) or simply induced cell death (assay at high density). The cellular density of the bacteria was then observed over a 48-h period. When added to dense cultures ($OD_{600} \approx 0.5$), no decrease in cell density was observed with any of the natural products, even at 5 mM concentrations (see Supporting Information Figure S10). Chloramphenicol, a well-documented antibiotic, was used as a positive control, and a significant decrease in bacterial density was observed at much lower concentrations of 0.05 mM (see Supporting Information). However, when the natural products were introduced to newly inoculated *E. coli* cultures, **5** and **8** prevented bacterial growth at 2 μM concentrations, and **10** at 3 mM concentrations. No growth inhibition was observed for **3** at even high concentrations (Figure 2).

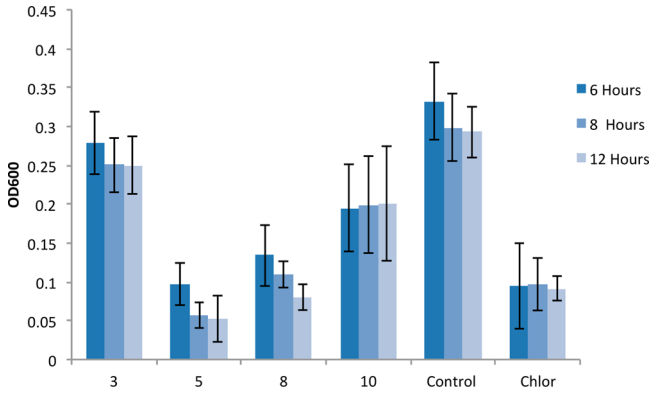


Figure 2. *E. coli* screens with natural products prepared via the solid-supported Glaser−Hay methodology. Cultures were inoculated at an OD_{600} of 0.1 and grown in the presence of the compounds at approximately 2 μM in a 96 well plate. The bacterial growth was monitored at 6, 8, and 12 h. A DMSO control exhibited significant culture growth, while a positive control of chloramphenicol at 0.05 mM exhibited no growth. All cultures were grown in triplicate to establish experimental error.

This suggests that these natural products do indeed possess antibacterial properties and can be easily prepared with the solid-supported Glaser−Hay methodology. Future work includes the use of more sophisticated bacterial assays to determine their mechanism of action and their investigation for other biological activity. Moreover, due to the modular synthesis, various analogs can be rapidly generated to conduct an extensive SAR study to further optimize their antibacterial properties. The application of the solid support also facilitates a

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wide range of combinatorial strategies to be employed toward the facile generation of large and varied polyyne libraries.

Overall, we have demonstrated that the solid-supported Glaser−Hay reaction is a useful methodology in the synthesis of natural products. The methodology has been employed to access four key natural products in fewer synthetic steps, higher yields, and with less purification. These natural products have been assessed for their antibacterial properties and found to be comparable in efficacy to traditional antibacterials such as choramphenicol.

EXPERIMENTAL SECTION

Immobilization of Alcohol onto Trityl Chloride Resin in Low Loading Conditions. Trityl chloride resin (200 mg, 0.36 mmol, 1 equiv) was added to a flame-dried vial charged with dichloromethane (5 mL). The resin was swelled at room temperature with gentle stirring for 15 min. Alcohol (25.0 μL, ∼1.2 equiv) was added to reaction, followed by triethylamine (10.0 μL, 0.072 mmol, 0.2 equiv). The mixture was stirred at room temperature for 16 h. The resin was transferred to a syringe filter and washed with DCM and MeOH (5 alternating rinses with 5 mL each). The resin was swelled in CH_2Cl_2 and dried under vacuum for 45 min before further use.

Polyyne Extension Protocol. Trimethylsilylacetylene (160 μL, 1.05 mmol, 15 equiv) was added to a flame-dried vial containing the alcohol derivatized trityl resin (100 mg, 0.07 mmol, 1 equiv) and tetrahydrofuran (2.0 mL). The CuI (20 mg, 1.06 mmol) and tetramethylethylenediamine (20 μL, 0.132 mmol) were added to a separate flame-dried vial and then dissolved in tetrahydrofuran (2.0 mL). The catalyst mixture was then added to the resin in one portion and stirred at 60 °C for 16 h. The resin was transferred to a syringe filter and washed with DCM and MeOH (5 alternating rinses with 5 mL each). The TMS group was then cleaved by incubation in 1 M tetra-*n*-butylammonium fluoride trihydrate in DCM (TBAF, 1 mL, 1 h). Then the reaction was again transferred to a syringe filter and washed with DCM and MeOH (5 alternating rinses with 5 mL each) and dried under vacuum for 45 min. Product was weighed and transferred to flame-dried vial for future use.

Dodeca-2,4-diyn-1-ol (3).[23] 1-Nonyne (115 μL, 0.70 mmol, 10 equiv) was added to a flame-dried vial containing the propargyl alcohol derivatized trityl resin (100 mg, 0.070 mmol, 1 equiv), and tetrahydrofuran (2 mL). CuI (10 mg, 0.053 mmol, ∼0.7 equiv) and tetramethylethylenediamine (30 μL) were added to a separate flame-dried vial and then dissolved in tetrahydrofuran (2 mL). The catalyst mixture was then added to the resin in one portion and stirred at 60 °C for 16 h. The resin was transferred to a syringe filter and washed with DCM and MeOH (5 alternating rinses with 5 mL each). The product was then cleaved from the resin by treatment with 1 mL of 2% TFA (DCM, 1 h) and filtered into a vial. A short silica plug was utilized to remove unreacted starting material (1:1 EtOAc/Hex), and pure product was obtained (0.010 g, 0.052 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.27 (s, 2H), 2.24 (t, J = 7.2 Hz, 2H), 1.55 (quint, J = 7.2 Hz, 2H), 1.39−1.31 (m, 2H), 1.30−1.19 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 51.7, 31.8, 29.5, 28.7, 28.1, 22.4, 19.2, 14.0. GC: t_R = 10.43 min; MS: m/z calcd for $C_{12}H_{18}O$ [M^+]: 178.136; found: 178.092.

Montiporic Acid A (5).[23] Ethyl bromoacetate (10 μL, 0.1 mmol, 2 equiv) was added at 10 °C to a vial containing **3** (0.010 g, 0.052 mmol, 1 equiv) dissolved in toluene (1 mL), 50% KOH (200 μL), and tetrabutyl ammonium sulfate (10 mg, 0.03 mmol, ∼0.5 equiv). The reaction was then vigorously stirred at 10 °C for 3 h. Upon completion, the reaction was quenched with dilute HCl (5 mL), extracted with EtOAc, and washed with H_2O (3 × 5 mL). The product was then dried over anhydrous $MgSO_4$, and solvent was removed *in vacuo*. Purification was performed via column chromatography (hexanes/EtOAc 10:1 to 1:3) to yield the desired product (8 mg, 0.039 mmol, 49%). ^{1}H NMR ($CDCl_3$: δ 4.38 (s, 2H), 4.21 (s, 2H), 2.24 (t, J = 7.2 Hz, 2H), 1.49 (quint, J = 7.2 Hz, 2H), 1.34−1.31 (m, 2H), 1.29−1.19 (m, 6H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 74.5, 71.1, 64.8, 64.6, 58.0, 51.5, 4.8; GC: t_R = 11.02 min; MS: m/z calcd for $C_{14}H_{20}O_3$ [M^+]: 236.141; found: 236.172

Octatriyn-1-ol (8).[26] The described polyyne extension protocol was used to obtain the immobilized terminal alkyne diyne. 1-Propyne (53 μL, 0.70 mmol, 10 equiv) was added to a flame-dried vial containing the immobilized resin (100 mg, 0.07 mmol, 1 equiv) and tetrahydrofuran (2 mL). The copper catalyst (10 mg, 0.053 mmol, ∼0.7 equiv) and tetramethylethylenediamine (30 μL) were added to a separate flame-dried vial then dissolved in tetrahydrofuran (2 mL). The catalyst mixture was then added to the resin reaction in one portion and stirred at 60 °C for 16 h. The resin was transferred to a syringe filter and washed with DCM and MeOH (5 alternating rinses with 3 mL each). The product was then cleaved from the resin by treatment with 1 mL 2% TFA (DCM, 1 h) and filtered into a vial. A short silica plug was performed to remove unreacted starting material (5:1 EtOAc/Hex), affording product **8** (4 mg, 0.040 mmol, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.70 (s, br, 1H), 4.34 (s, 2H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 74.2, 71.1, 65.0, 64.8, 58.4, 51.7, 4.5; GC: t_R = 10.99 min; MS: m/z calcd for C_8H_6O [M^+]: 118.042; found: 118.051

Phenylhepta-2,4,6-triynyl Acetate (10).[26] The described polyyne extension protocol was used to obtain the immobilized terminal alkyne diyne. Phenylacetlyene (0.70 mmol, 10 equiv) was added to a flame-dried vial containing the starting material (100 mg, 0.070 mmol, 1 equiv) and tetrahydrofuran (2 mL). The CuI (10 mg, 0.053 mmol) and tetramethylethylenediamine (30 μL) were added to a separate flame-dried vial and then dissolved in tetrahydrofuran (2 mL). The catalyst mixture was then added to the resin reaction in one portion and stirred at 60 °C for 16 h. The resin was transferred to a syringe filter and washed with DCM and MeOH (5 alternating rinses with 5 mL each). The product was then cleaved from the resin by treatment with 1 mL of 2% TFA (DCM, 1 h) and filtered into a vial. Solvent was removed *in vacuo* to afford the free alcohol (10 mg, 0.056 mmol, 80%). Acetic anhydride (1 mL) and a catalytic amount of DMAP were added and dissolved in 1 mL of DCM. The reaction was allowed to stir at room temperature for 3 h, followed by an extraction using DCM/H_2O (3 × 5 mL) and drying with $MgSO_4$. The product was then purified on a silica gel column using 5:1 Hex/EtOAc yielding **10** (9 mg, 0.041 mmol, 46%), which was then analyzed via ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70−7.61 (m, 2H), 7.56−7.32 (m, 3H), 4.85 (s, 2H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 171.0, 134.5, 131.5, 129.9, 121.2, 78.5, 76.3, 74.3, 70.8, 66.2, 63.8, 53.1, 20.9; GC: t_R = 9.89 min; MS: m/z calcd for $C_{15}H_{10}O_2$ [M^+]: 222.068; found: 222.079.

Low Cell Density Absorbance Assay. Luria−Bertani (LB) media (10 mL) was inoculated with the *Escherichia coli* Novagen BL21(DE3) strain of cells and then incubated for 16 h at 37 °C. Optical density measurements on a spectrophotometer at 600 nm (OD_{600}) was used to assess the density of the starter culture. The culture was diluted to an OD_{600} of 0.1 (low density) by addition of fresh LB media. In a new 96 well microplate (Greiner Bio-One), the solutions of varying concentration for each product from the working plate were plated including chloramphenicol and DMSO (20 μL). Subsequently, the low density cell solution was added to each well in which solution had been previously added. An initial absorbance was read using a Synergy HT Microplate Reader set to shake the plate for 10 s prior to reading the OD_{600}. An absorbance reading was taken again at 2, 4, 6, 8, 12, and 24 h. Between OD_{600} readings the microplate was allowed to shake at 37 °C.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02407.

Supplemental experimental protocols, ^{1}H and ^{13}C NMR data, GC data, and low and high density biological assay results (PDF)

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Notes

The authors declare no competing financial interest.

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