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Note

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Synthesis of the Marine Myxobacterial Antibiotic Enhygrolide A

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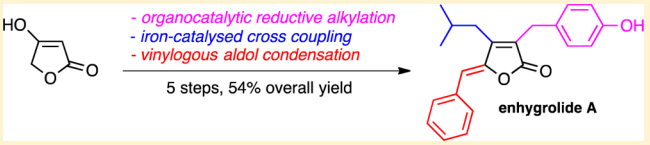
Supporting Information

ABSTRACT: The first synthesis of enhygrolide A, a scarce γ-alkylidenebutenolide antibiotic of the obligate marine myxobacterium *Enhygromyxa salina*, was achieved in five steps and 54% overall yield from tetronic acid. Key steps include (i) organocatalytic reductive alkylation, (ii) iron-catalyzed sp^2–sp^3 cross-coupling, and (iii) vinylogous aldol condensation. Aside from its brevity and reliance on environmentally sustainable processes, the synthesis demonstrates the serviceability of butenolide pivalates in cross-coupling reactions.



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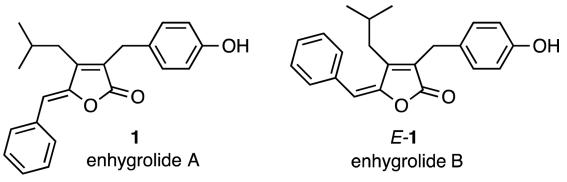
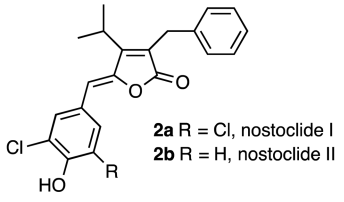
The relentless rise in antibiotic resistance has created an urgent need for new antimicrobials.[1] Nature's genetically encoded small molecules have traditionally been, and still are, the best starting point for antibiotic development.[2] Currently, over 60% of all clinically used antibiotics come from Gram-positive, cultivable soil bacteria of the order Actinomycetales (cf. terrestrial actinomycetes).[3] Although these microbes continue to be studied today,[4] the search for new metabolites has met with diminishing returns, leading too often to rediscovery of known compounds.[2,4a] As a result, growing attention is being focused on new reservoirs of biodiversity, particularly the microbial communities of marine ecosystems.

Myxobacteria are unique Gram-negative organisms having larger genomes than other taxa of bacteria and as such are capable of producing a variety of bioactive metabolites that are not found in actinomycetes or fungi.[5] While myxobacteria dwell in both soil and water habitats, these microbes were largely unrecognized in the world's oceans until recently. Further, because marine myxobacteria are notoriously difficult to isolate and cultivate, only a handful of their secondary metabolites have been identified to date.[5,6]

In 2013, König and her group reported the discovery of three new antibiotics from the hitherto unexplored marine myxobacterium *Enhygromyxa salina*.[6,7] The most potent of them, enhygrolide A (**1**), exhibited an MIC of 4 μg/mL against *Arthrobacter crystallopoietes*.[6] Structurally, enhygrolide A features a privileged, densely substituted (*Z*)-γ-ylidenebutenolide motif reminiscent of the cyanobacterial metabolites nostoclides I and II (**2a**,**b**).[8−10] Unlike the nostoclides, enhygrolide A was obtained along with its *E*-isomer, enhygrolide B (*E*-**1**), although the latter could not be isolated in pure form due to conversion into the more stable *Z*-isomer **1**.[6] Interestingly, many compounds from this class, natural or otherwise, are endowed with diverse biological properties including antimicrobial,[10a,11a] antitumor,[11b] antidiabetic,[11c] and herbicidal activities.[10b] Unfortunately, the extreme scarcity of **1** (0.7 mg from 64 L of culture)[6] precluded more profound biological studies. This and the unprecedented carbon skeleton of **1** prompted us to undertake its synthesis.





Previous total[9a,d] and formal[9b,c] syntheses of the related nostoclides, including our own,[9a] fall short of the ideal for several reasons including (i) modest efficiency of cross-coupling regimens for installing the benzyl moiety onto butenolide[9b,d] or maleic anhydride precursors[9c] and (ii) reliance on expensive or inaccessible starting materials and reagents, notably 2-furyl *N*,*N*,*N*′,*N*′-tetramethyldiamidophosphate[9a] and benzyl trifluoroboronates.[9d] We therefore sought to establish a new pathway to these targets (cf. **A**), based on the strategy shown in Scheme 1.

Tetronic acid (**3**) was viewed as an inexpensive source of the butenolide nucleus onto which the appropriate benzyl, alkyl, and benzylidene substituents would be appended sequentially by means of reductive alkylation, iron-catalyzed cross-coupling,

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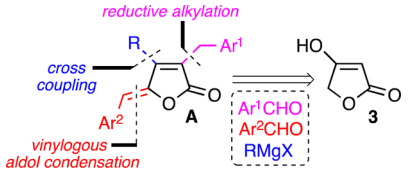
Scheme 1. Retrosynthesis



and vinylogous aldol condensation (VAC). Besides the butenolide ring, all carbon substituents in **A** would derive from simple, readily available chemicals (cf. benzaldehydes and RMgX, Scheme 1). Reported herein is the successful implementation of this plan to the first synthesis of enhygrolide A (**1**).

As shown in Scheme 2, the synthesis began by subjecting **3** to reductive alkylation with *p*-methoxybenzaldehyde **4** using an organocatalytic method developed by Ramachary.[12] In doing so, gram quantities of the known lactone **5**[13] were obtained in a single operation and substantially higher yield than the current two-step procedure[13] (83% vs 55−63%).

Prior work in the group[14] suggested that iron-catalyzed cross-coupling of butenolide triflates with Grignard reagents[15] offered an appealing alternative to the Suzuki reaction for introducing the isobutyl substituent. In the present instance, reaction of triflate **6a** with *i*-BuMgBr under slightly modified Fürstner conditions[14,16] (10% mol $Fe(acac)_3$, *N*-methylpyrrolidone/tetrahydrofuran (THF), −40 °C, 1 h) provided butenolide **7** in a respectable yield of 69% (Scheme 2). While other iron catalysts and conditions were somewhat less effective, switching to the more robust pivalate leaving group[17] proved highly rewarding. Indeed, under optimal, ligand-free conditions and lower catalyst loading (2% mol $FeCl_2$, THF, 0 °C, 1 h), coupling of pivalate **6b** with *i*-BuMgBr was remarkably clean, affording **7** in 93% yield after flash chromatography. This is the first cross-coupling reaction of a butenolide pivaloate.

With **7** in hand, the time had come to install the *Z*-configured benzylidene moiety and thus generate **8** (Scheme 2). In general, VAC reactions of butenolides having a bulky *β*-substituent, such as Ar, *i*-Pr, or Br, lead to *Z*-products,[18] whereas those bearing small substituents (e.g., Me) provide *Z*/*E* mixtures.[19] As the isobutyl group in **7** falls in between these categories, we were pleased to find that the desired VAC led uniquely to the *Z*-isomer, regardless of the method employed (TBSOTf/DIPEA/DBU/CH_2Cl_2,[18a] piperidine,[18b] or sodium carbonate[19a] in MeOH). Further, the latter procedure[19a] proved responsive to optimization (50 °C, 24 h), affording **8** in a reproducible 82% yield. Finally, methyl ether cleavage with boron tribromide smoothly led to enhygrolide A (**1**, Scheme 2), whose ^1H and ^{13}C NMR spectra were in excellent agreement with those reported in the literature.[6]

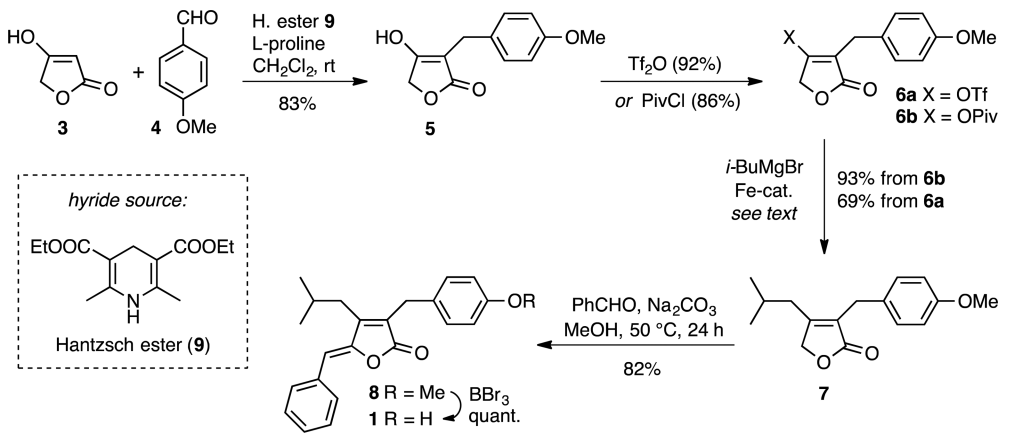
In the course of our work, we also explored the feasibility of converting **1** to enhygrolide B (*E*-**1**) by means of photoisomerization. Such a process has reportedly enabled 72% conversion of a similarly substituted (*Z*)-*γ*-ylidenebutenolide to its *E*-isomer.[20] In the present instance, exposure of a $CDCl_3$ solution of **1** to light for 6−8 days at room temperature afforded a 3:2 mixture of the *Z*/*E*-isomers, essentially free from side-products. Likewise, clean photoequilibration could be achieved in acetonitrile, albeit still in favor of the *Z*-isomer (**1**/*E*-**1** ca. 2:1).

To conclude, the first synthesis of enhygrolide A (**1**), a rare antibiotic of the obligate marine myxobacterium *E. salina*, was accomplished in five steps and 54% overall yield from commercially available tetronic acid. The route is efficient and scalable, relies on green processes and inexpensive reagents, and demonstrates, for the first time, the exceptional performance of a butenolide pivaloate in iron-catalyzed cross-coupling. Work to expand and apply this technology to the construction of related natural products is under way, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined in open capillary tubes using a Barnstead Electrothermal Mel-Temp 1201D apparatus and are uncorrected. Infrared spectra were recorded on a Bomem Arid Zone MB-series FTIR instrument, with samples prepared on single NaCl plates. NMR was recorded on an Agilent DD2 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C nuclei. Electrospray ionization (ESI) high-resolution mass spectra were recorded on a time-of-flight Agilent 6210 TOF LC/MS instrument. The following procedures were used unless otherwise noted. Moisture-sensitive reactions and dry solvent distillation were carried out in flame-dried glassware sealed under a positive pressure of dry argon. Moisture-sensitive liquids, solutions, and anhydrous solvents were transferred by syringe or cannula through rubber septa. Commercial reagents were used as received except for Hünig's base, which was distilled from KOH pellets. Prior to use, dry THF was distilled from sodium/acetophenone and dry CH_2Cl_2 was distilled from calcium hydride. Reactions were monitored by thin layer chromatography (TLC) carried out on Merck 0.2 mm silica gel 60 F254 aluminum-backed plates. Flash column chromatography was

Scheme 2. Total Synthesis of Enhygrolide A (1)



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performed on a Teledyne Isco Combi-flash Rf-200 UV−vis using Silicycle silica gel 60 (230−400 mesh) as stationary phase.

4-Hydroxy-3-(4-methoxybenzyl)furan-2(5*H*)-one (5). A solution of **3** (502 mg, 5.02 mmol, 1.0 equiv), aldehyde **4** (2.05 g, 15.06 mmol, 3.00 equiv), and Hantzsch ester **9** (1.27 g, 5.02 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) and L-proline (28.9 mg, 0.25 mmol, 0.05 equiv) was added, and the reaction mixture was stirred for 12 h at rt. The volatiles were evaporated under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 80:20) to give **5** (920 mg, 83%) as a yellow solid: mp 161−162 °C; IR (NaCl, film) ν_{max} 2984, 2691, 1771, 1456, 1361, 1248, 1098, 1027, 789 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 7.17 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.63 (s, 2H), 3.74 (s, 3H), 3.43 (s, 2H), 3.18 (br s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 175.3, 173.1, 159.0, 132.3, 130.1, 114.4, 101.4, 67.2, 55.4, 26.8; HRMS (ESI-TOF) m/z 221.0807 $[M + H]^+$ (calcd for $C_{12}H_{13}O_4$ 221.0808); anal. calcd for $C_{12}H_{12}O_4$, C, 65.45; H, 5.49; found C, 65.54; H, 5.67.

4-(4-Methoxybenzyl)-5-oxo-2,5-dihydrofuran-3-yl Trifluoromethanesulfonate (6a). A solution of **5** (630 mg, 2.86 mmol, 1.0 equiv) and Hünig's base (1.0 mL, 5.72 mmol, 2.0 equiv) in dry CH_2Cl_2 (40 mL) was cooled to −40 °C. Trifluoromethanesulfonic anhydride (0.63 mL, 3.72 mmol, 1.3 equiv) was added dropwise over 10 min. After stirring for 50 min at −40 °C, TLC indicated complete consumption of starting material, at which point H_2O (100 mL) was added and the temperature allowed to rise to room temperature (rt). Once all the ice had melted, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (hexanes/EtOAc, 90:10) furnished **6a** (932 mg, 92%) as a bright orange oil: IR (NaCl, film) ν_{max} 2840, 1773, 1514, 1250, 1222, 1136, 811, 609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.92 (s, 2H), 3.78 (s, 3H), 3.60 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 160.4, 158.9, 129.9, 127.4, 119.8, 119.7, 118.4 (q, $^1J_{C-F}$ = 321.2 Hz), 114.4, 66.4, 55.4, 27.7; HRMS (ESI-TOF) m/z 353.0290 $[M + H]^+$ (calcd for $C_{13}H_{12}F_3O_6S$ 353.0301); anal. calcd for $C_{13}H_{11}F_3O_6S$, C, 44.32; H, 3.15; found C, 44.44; H, 3.11.

4-(4-Methoxybenzyl)-5-oxo-2,5-dihydrofuran-3-yl Pivalate (6b). To a stirred solution of **5** (195.1 mg, 0.89 mmol, 1.0 equiv), 4-(N,N-dimethylamino)pyridine (5.4 mg, 0.04 mmol, 0.05 equiv), and Hünig's base (0.16 mL, 0.93 mmol, 1.05 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added neat pivaloyl chloride (0.11 mL, 0.93 mmol, 1.05 equiv) dropwise, and the mixture was allowed to warm to rt. After stirring for 16 h, the mixture was concentrated in vacuo to give an amber oil. The oil was dissolved in CH_2Cl_2 (30 mL) and washed with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by flash column chromatography (hexanes/EtOAc, 80:20) to provide **6b** (233.0 mg, 86%) as colorless crystals: mp 39−41 °C; IR (NaCl, film) ν_{max} 2977, 2837, 1766, 1686, 1512, 1248, 1102, 1071, 855, 788, 752, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.10 (s, 2H), 3.77 (s, 3H), 3.53 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 172.6, 164.5, 158.5, 129.7, 129.6, 114.2, 112.5, 68.1, 55.4, 39.5, 27.7, 26.9; HRMS (ESI-TOF) m/z 305.1390 $[M + H]^+$ (calcd for $C_{17}H_{21}O_5$ 305.1383).

4-Isobutyl-3-(4-methoxybenzyl)furan-2(5*H*)-one (7). Pivalate **6b** (105.8 mg, 0.35 mmol, 1.0 equiv) and $FeCl_2$ (0.88 mg, 0.007 mmol, 2 mol %) were added to dry and degassed THF (3 mL), and the reaction mixture was cooled to 0 °C. The mixture was stirred for 10 min at this temperature, and isobutylmagnesium bromide (0.42 mL of a 2 M in Et_2O, 0.84 mmol, 2.4 equiv) was rapidly added. There was an immediate color change from light brown to black-brown. The mixture was left stirring for 50 min at 0 °C and then quenched with saturated NH_4Cl(aq) (4 mL). The mixture was partitioned between H_2O (20 mL) and Et_2O (20 mL) and extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a brown residue. Purification by flash column chromatography (hexanes/EtOAc, 80:20) gave **7** (84.9 mg, 93%) as a colorless oil: IR (NaCl, film) ν_{max} 2957, 1749, 1558, 1512, 1464, 1248, 793 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.65 (s, 2H), 3.76 (s, 3H), 3.54 (s, 2H), 2.31 (d, J = 7.5 Hz, 2H), 1.74−1.85 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 160.9, 158.2, 130.3, 129.5, 127.2, 114.0, 71.7, 55.3, 36.4, 28.7, 27.8, 22.7; HRMS (ESI-TOF) m/z 261.1480 $[M + H]^+$ (calcd for $C_{16}H_{21}O_3$ 261.1485).

(*Z*)-5-Benzylidene-4-isobutyl-3-(4-methoxybenzyl)furan-2(5*H*)-one (8). Butenolide **7** (102.4 mg, 0.39 mmol, 1.0 equiv) and anhydrous Na_2CO_3 (41.7 mg, 0.39 mmol, 1.0 equiv) were dissolved in MeOH (4.0 mL), and then benzaldehyde (62.6 mg, 0.59 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C for 24 h. The mixture was concentrated under reduced pressure and purified by flash column chromatography (hexanes/EtOAc, 90:10) to afford **8** (111.8 mg, 82%) as a white solid: mp 86−88 °C; IR (NaCl, film) ν_{max} 2957, 1770, 1558, 1508, 1457, 1247, 970, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 6.01 (s, 1H), 3.78 (s, 3H), 3.69 (s, 2H), 2.43 (d, J = 7.5 Hz, 2H), 1.89−2.01 (m, 1H) 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 158.4, 152.5, 148.8, 133.2, 130.5, 129.8, 129.6, 128.8, 128.8, 127.3, 114.1, 109.6, 55.3, 33.9, 29.4, 29.0, 22.9; HRMS (ESI-TOF) m/z 349.1808 $[M + H]^+$ (calcd for $C_{23}H_{25}O_3$ 349.1798); anal. calcd for $C_{23}H_{24}O_3$, C, 79.28; H, 6.94; found C, 79.60; H, 7.23.

Enhygrolide A (1). To a solution of **8** (78.5 mg, 0.23 mmol, 1.0 equiv) in dry CH_2Cl_2 (4 mL) was added BBr_3 (0.34 mL of a 1 M in CH_2Cl_2, 0.34 mmol, 1.5 equiv) at 0 °C. The mixture was stirred for 2 h at that temperature, quenched with saturated $NaHCO_3$(aq) (5 mL), and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 70:30) to give **1** (76.9 mg, 100%) as a greenish, amorphous solid: IR (NaCl, film) ν_{max} 3384, 2928, 2869, 1770, 1558, 1449, 1264, 971, 675 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.80 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 6.25 (s, 1H), 3.65 (s, 2H), 2.50 (d, J = 7.5 Hz, 2H), 1.84−2.00 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.0, 157.0, 154.2, 149.8, 134.6, 131.4, 130.3, 129.9, 129.6, 128.3, 116.2, 110.9, 34.2, 30.3, 29.5, 22.8; HRMS (ESI-TOF) m/z 335.1631 $[M + H]^+$ (calcd for $C_{22}H_{23}O_3$ 335.1641); anal. calcd for $C_{22}H_{22}O_3$, C, 79.02; H, 6.63; found C, 79.37; H, 6.89.

Photoisomerization of Enhygrolide A (1). A solution of **1** (23.0 mg, 0.07 mmol) in $CDCl_3$ (3.0 mL) was irradiated with a halogen light bulb (500 W, 130 V; placed at a distance of 96 cm) under stirring for 7 days at rt. The solvent was evaporated under reduced pressure to give a 3:2 mixture of **1** and *E*-**1** (23.0 mg, 100%). Their respective identities were established by integration of diagnostic NMR signals (^1H NMR (500 MHz, CD_3OD) δ_Z 6.24, 3.64, 2.50, 0.95; δ_E 6.89, 3.59, 2.30, 0.45; ^{13}C NMR (125 MHz, CD_3OD) δ_Z 172.2, 154.4, 129.6, 111.0; δ_E 171.7, 151.6, 133.4, 116.4 ppm) and comparison with the reported values for naturally derived samples.[6] When the same procedure was performed using MeCN as a solvent, a 2:1 mixture of **1** and *E*-**1** (100%) was obtained.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00405.

^1H and ^{13}C NMR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Brown, E. D.; Wright, G. D. *Nature* **2016**, *529*, 336−343. (b) Kretz, J.; Kerwat, D.; Schubert, V.; Grätz, S.; Pesic, A.; Semsary, S.; Cociancich, S.; Royer, M.; Süssmuth, R. D. *Angew. Chem., Int. Ed.* **2015**, *54*, 1969−1973.

(2) (a) Ling, L. L.; Schneider, T.; Peoples, A. J.; Spoering, A. L.; Engels, I.; Conlon, B. P.; Mueller, A.; Schäberle, T. F.; Hughes, D. E.; Epstein, S.; Jones, M.; Lazarides, L.; Steadman, V. A.; Cohen, D. R.; Felix, C. R.; Fetterman, K. A.; Millett, W. P.; Nitti, A. G.; Zullo, A. M.; Chen, C.; Lewis, K. *Nature* **2015**, *517*, 455−459. (b) Kolter, R.; van Wezel, G. P.; Kolter, R.; van Wezel, G. P. *Nat. Microbiol.* **2016**, *1*, 15020.

(3) (a) Barka, E. A.; Vasta, P.; Sanchez, L.; Gaveau-Vaillant, N.; Jacquard, C.; Klenk, H.-P.; Clément, C.; Ouhdouch, Y.; van Wezel, G. P. *Microbiol. Mol. Biol. Rev.* **2016**, *80*, 1−43. See also: (b) Boukouvalas, J.; Loach, R. P. *Org. Lett.* **2013**, *15*, 4912−4914.

(4) Examples: (a) Lu, S.; Nishimura, S.; Ito, M.; Tsuchida, T.; Kakeya, H. *J. Nat. Prod.* **2016**, *79*, 1891−1895. (b) Sheng, Y.; Lam, P. W.; Shahab, S.; Santosa, D. A.; Proteau, P. J.; Zabriskie, T. M.; Mahmud, T. *J. Nat. Prod.* **2015**, *78*, 2768−2775. (c) Pesic, A.; Steinhaus, B.; Kemper, S.; Nachtigall, J.; Kutzner, H. J.; Höfle, G.; Süssmuth, R. D. *J. Antibiot.* **2014**, *67*, 471−477. (d) Shin, B.; Kim, B.-Y.; Cho, E.; Oh, K.-B.; Shin, J.; Goodfellow, M.; Oh, D.-C. *J. Nat. Prod.* **2016**, *79*, 1886−1890.

(5) (a) Recent review: Dávila-Céspedes, A.; Hufendiek, P.; Cruüsemann, M.; Schäberle, T. F.; König, G. M. *Beilstein J. Org. Chem.* **2016**, *12*, 969−984. (b) Sun, Y.; Feng, Z.; Tomura, T.; Suzuki, A.; Miyano, S.; Tsuge, T.; Mori, H.; Suh, J.-W.; Iizuka, T.; Fudou, R.; Ojika, M. *Sci. Rep.* **2016**, *6*, 22091.

(6) Felder, S.; Kehraus, S.; Neu, E.; Bierbaum, G.; Schäberle, T. F.; König, G. M. *ChemBioChem* **2013**, *14*, 1363−1371.

(7) Felder, S.; Dreisigacker, S.; Kehraus, S.; Neu, E.; Bierbaum, G.; Wright, P. R.; Menche, D.; Schäberle, T. F.; König, G. M. *Chem. - Eur. J.* **2013**, *19*, 9319−9324.

(8) Yang, X.; Shimizu, Y.; Steiner, J. R.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 761−764.

(9) Synthesis of nostoclides: (a) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897−7900. (b) Bellina, F.; Rossi, R. *Synthesis* **2002**, 2729−2732. (c) Kar, A.; Gogoi, S.; Argade, N. P. *Tetrahedron* **2005**, *61*, 5297−5302. (d) Ngi, S. I.; Petrignet, J.; Duwald, R.; El Hilali, E. M.; Abarbri, M.; Duchêne, A.; Thibonnet, J. *Adv. Synth. Catal.* **2013**, *355*, 2936−2941.

(10) Bioactive nostoclide analogues: (a) Barbosa, L. C. A.; Maltha, C. R. A.; Demuner, A. J.; Pinheiro, P. F.; Varejão, J. O. S.; Montanari, R. M.; Andrade, N. J. *Quim. Nova* **2010**, *33*, 2020−2026. (b) Barbosa, L. C. A.; Varejão, J. O. S.; Petrollino, D.; Pinheiro, P. F.; Demuner, A. J.; Maltha, C. R. A.; Forlani, G. *Arkivoc* **2012**, No. v, 15−32.

(11) (a) Wang, W.; Kim, H.; Nam, S.-J.; Rho, B. J.; Kang, H. *J. Nat. Prod.* **2012**, *75*, 2049−2054. (b) Liu, G.-Z.; Xu, H.-W.; Wang, P.; Lin, Z.-T.; Duan, Y.-C.; Zheng, J.-X.; Liu, H.-M. *Eur. J. Med. Chem.* **2013**, *65*, 323−336. (c) Boukouvalas, J.; McCann, L. C. *Tetrahedron Lett.* **2010**, *51*, 4636−4639 and cited references.

(12) Ramachary, D. B.; Kishor, M. *Org. Biomol. Chem.* **2010**, *8*, 2859−2867.

(13) (a) Schröder, P.; Bauer, J. O.; Strohmann, C.; Kumar, K.; Waldmann, H. *J. Org. Chem.* **2016**, *81*, 10242−10255. (b) Pashkovskii, F. S.; Shchukina, E. M.; Gribovskii, M. G.; Lakhvich, F. A. *Russ. J. Org. Chem.* **2008**, *44*, 657−670.

(14) Boukouvalas, J.; Albert, V.; Loach, R. P.; Lafleur-Lambert, R. *Tetrahedron* **2012**, *68*, 9592−9597.

(15) Recent reviews: (a) Legros, J.; Figadère, B. *Nat. Prod. Rep.* **2015**, *32*, 1541−1555. (b) Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170−3387. (c) Guérinot, A.; Cossy, J. *Top. Curr. Chem.* **2016**, *374*, No. 49, DOI: 10.1007/s41061-016-0047-x.

(16) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943−3949.

(17) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656−14657.

(18) (a) Boukouvalas, J.; Beltrán, P. P.; Lachance, N.; Côté, S.; Maltais, F.; Pouliot, M. *Synlett* **2007**, *2007*, 219−222 and cited references. (b) Boukouvalas, J.; Thibault, C. *J. Org. Chem.* **2015**, *80*, 681−684. (c) Acosta, J. A. M.; Muddala, R.; Barbosa, L. C. A.; Boukouvalas, J. *J. Org. Chem.* **2016**, *81*, 6883−6886.

(19) (a) Yu, B.; Zhang, E.; Fang, Y.; Sun, X.-N.; Ren, J.-L.; Yu, D.-Q.; Liu, H.-M. *Heterocycles* **2013**, *87*, 163−176. (b) Thombal, R. S.; Jadhav, V. H. *Org. Biomol. Chem.* **2015**, *13*, 9485−9491.

(20) Pignatello, J. J.; Porwoll, J.; Carlson, R. E.; Xavier, A.; Gleason, F. K.; Wood, J. M. *J. Org. Chem.* **1983**, *43*, 4035−4038.

DOI: 10.1021/acs.jnatprod.7b00405
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