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Communication

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Kyle S. McClymont, Feng-Yuan Wang, Amin Minakar, and Phil S. Baran

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Total Synthesis of (–)-Maximiscin

Kyle S. McClymont, Feng-Yuan Wang, Amin Minakar, and Phil S. Baran*

Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information Placeholder

ABSTRACT: A short, enantioselective synthesis of (–)-maximiscin, a structurally-intriguing metabolite of mixed biosynthetic origin, is reported. A retrosynthetic analysis predicated on maximizing ideality and efficiency led to several unusual disconnections and tactics. Formation of the central highly-oxidized pyridone ring through a convergent coupling at the end of the synthesis simplified the route considerably. The requisite building blocks could be prepared from feedstock materials (derived from shikimate and mesitylene). Strategies rooted in hidden symmetry recognition, C–H functionalization, and radical retrosynthesis played key roles developing this concise route.

Natural products derived from mixed biosynthetic lineages have historically provided chemists with some of the most exotic molecular architectures imaginable (*e.g.* staurosporine, hyperforin, and reserpine).[1] The unique structure of (–)-maximiscin **1** (Figure 1A) is no exception, resulting from the rare union of three separate metabolic pathways.[2] Thus, a central 1,4-dihydroxy-2-pyridone (derived from tyrosine **3**) is linked to both a shikimate derivative (derived from shikimic acid **2**) and a trisubstituted cyclohexyl fragment of polyketide origin (derived from **4**). As such, **1** exists as an equilibrating mixture of atropisomers about the C-3,7 bond. The challenge associated with synthesizing such a structure is compounded by its documented instability, as it tends to fragment between the shikimate and pyridone residues.[3] 4-hydroxy-2-pyridone alkaloids such as **1** have historically represented an exciting class of natural products for chemical synthesis, due to their intriguing structural properties, and biological activiites.[4] Although no synthesis of **1** has been reported, simpler variants lacking the shikimate subunit have been prepared.[5] In this Communication, an abiotic, convergent, enantioselective preparation of **1** is reported; this synthesis is enabled by exploiting hidden symmetry and leveraging the logic of C–H functionalization[6] and radical retrosynthesis strategies[7].

To maximize convergency, retrosynthetic scission of the central pyridone ring produced two equally sized fragments (R=shikimate derivative **5**, and **6**). Their union through a non-canonical Guareschi-Thorpe-type condensation (Tactic 1, Figure 1B) could potentially forge this core motif at a late-stage. While such condensations normally require an electron-withdrawing group on the enamine fragment,[8] in this variant a β-silicon atom was employed, reminiscent of the Sakurai-type allylation.[9] This provided the added benefit of building in the requisite *N*-oxide motif, which would otherwise require subsequent oxidation from the parent pyridone.[5, 10] Fragment **5** could be traced back to a known shikimate-derived epoxide in a few simple steps. Fragment **6** was envisaged to arise from a decarboxylative radical homologation sequence (Tactic 2) to forge the hindered C-3,7-bond and set its relative *trans*-orientation. During this process, a remarkably efficient radical cascade was developed to achieve not only this bond formation but also a redox relay[11] to set the proper C-13 oxidation state. Recognizing that if the C-13 position were simply a methyl group, an enantiocontrolled desymmetrizing C–H activation could be invoked (Tactic 3) to cement the absolute configuration of *four* centers in one step.[12] Such a tactic is not without risk, as the required C-H activation would enlist a challenging 6-membered palladacycle intermediate.[13] Finally, the all-*cis* stereochemistry needed for this step could originate from the hydrogenation of an inexpensive mesitylene-derived carboxylic acid **7**[14] (Tactic 4).

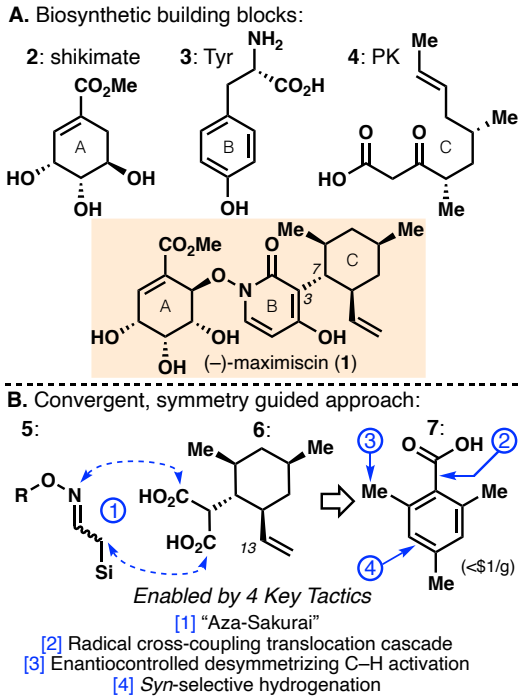

Figure 1. (A) (–)-Maximiscin (**1**): biosynthesis; (B) key strategies and tactics employed.

The successful execution of these tactics to access synthetic **1** for the first time is outlined in Scheme 1. Preparation of fragment **6** (Scheme 1A) began with hydrogenation of **7** using Adam's catalyst, which furnished the all-*cis* carboxylic acid **8** with complete selectivity in 97% isolated yield (gram-scale).[15] This set the stage for the development of a desymmetrizing C–H activation reaction that was to define four chiral centers from this *meso*-acid.[16] An exhaustive set of directing groups and C–H functionalization conditions were explored (see SI), culminating in the identification

of a chiral PIP-type directing group (**9**, X = H, inset table 1).[17] Amide **10d**, derived from acid **8** and amine **9** (84% isolated yield, gram-scale), conferred reasonable yield and high diastereoselectivity under Pd-catalyzed methoxylation conditions to deliver **11**.[18] The influence of various substituents on the pyridyl ring of the directing group was then explored. Although diastereoselectivity remained high, ring electronics exerted a profound effect on reaction yield (inset table 1). A 4-Cl substituted analog was identified as the optimal directing group, and upon further refinement of the reaction conditions, a scalable desymmetrizing methoxylation to access **11** was realized (58% isolated yield + 23% recovered **10d**, gram-scale). This, to the best of our knowledge, represents the most complex desymmetrizing C–H activation reported to-date.[19] It defines 4 stereocenters in a single step, including the distal δ-methyl substituent, which is remote from the directing group. Removal of the directing group from **11** was accomplished using HBr at elevated temperature (99% isolated yield, gram-scale). This reaction cleanly delivered lactone **12**, along with a substantial amount of recovered directing group **9** (80%). The latter material could be recycled, and used to prepare another batch of amide **10d** for the C–H activation sequence, without any erosion in enantiopurity (see SI). With lactone **12** in hand, the next tactic involved effecting a decarboxylative homologation for a key C–C bond forming step, drawing further utility from the C–H functionalization handle. Phenyl vinyl sulfone was selected as the homologation reagent of choice. It represents a simple, inexpensive 2-carbon extension unit, and has precedent for such applications.[20] Initial success was achieved using a Ni-catalyzed decarboxylative Giese addition protocol[21] (performed on a derivative of **12**, see SI), but the yield was hampered by competing 1,5-hydrogen atom transfer (1,5-HAT) from C–2 to C–13 which resulted in double addition of the radical acceptor onto C–13 (see SI). It was hypothesized that transitioning from a reductive to oxidative decarboxylative manifold could enable this transposed radical to be oxidized, thus producing aldehyde **14**.[22] A number of exotic redox strategies were evaluated before a simple solution emerged (see SI) using Minisci-type conditions[23] directly from lactone **12**, which was hydrolyzed *in-situ*. Thus, following saponification of lactone **12** with NaOH (1.2 equiv), sequential addition of $AgNO_3$ (0.3 equiv), $Na_2S_2O_8$ (2.5 equiv), $NaHSO_4$ (1.13 equiv), $Fe_2(SO_4)_3$ (0.2 equiv), and the vinyl sulfone led to the formation of aldehyde **14**. The reaction was exceptionally clean (see SI for crude NMR) and proved scalable, resulting in a 91% yield of **14** on gram scale. Some features of this radical translocation cascade are worth noting. The addition of $NaHSO_4$ enabled the tandem hydrolysis/decarboxylation by buffering the resulting carboxylate. Without it, a heterogeneous mixture resulted, leading to aggregate formation and diminished product yield. The standard Ag^+/persulfate combination proved ineffective (ca. 6% yield), prompting the exploration of additives (inset table 2). $Fe_2(SO_4)_3$ uniquely served as a highly efficient co-catalyst, the first use we are aware of in concert with a Ag-catalyzed Minisci-reaction.[24] The reaction requires both metals to be present, as no desired product is formed in the absence of Ag. Literature on the reactivity of Fe-salts in free radical chemistry suggest that the Fe^{3+} can assist in the selective oxidation of the intermediate α-oxy alkyl radical.[25] With aldehyde **14** in hand, access to key building block **6** could be rapidly achieved. Classical Wittig conditions provided an olefin intermediate which was elaborated to **15** through a one-pot sulfone oxidation and methyl ester formation sequence (50% yield overall).[26] Next, acylation of **15** proved challenging, with most acyl electrophile/base combinations leaving the hindered ester untouched. Use of LDA with Mander's reagent in diethyl ether proved uniquely effective,[27] and *in-situ* hydrolysis of the resulting diester provided **6** in 74% isolated yield. The crude diacid could be purified by simple trituration, and yielded crystals suitable for x-ray diffraction, which confirmed its absolute configuration.

Synthesis of fragment **5** was accomplished starting from known epoxide **16**, which is derived from shikimic acid (Scheme 1B).[28] Opening of the epoxide intermediate to furnish **17** was achieved using *N*-Boc-hydroxylamine assisted by DBU in methylene chloride (70% isolated yield, gram-scale); use of Lewis acids led to mixtures of S_N2/S_N2' products, while elimination/aromatization pathways dominated in different solvents. X-ray analysis confirmed the regioselectivity of the epoxide opening process. Intermediate **17** was converted to a TBS-protected hydroxylamine intermediate (72% isolated yield, gram-scale), which was condensed with acetaldehyde to give **des-TMS-5** (not shown, 82% isolated yield). The final bond-forming step involved union of this fragment with **6** using a bold late-stage pyridone synthesis to forge the central ring of **1**. Initial conditions surveyed for this step were based on a report for the synthesis of alkyl-fused hydroxypyridones, derived from diacid chlorides and ketoxime ethers.[29] Combination of oxime ether **des-TMS-5** with the diacid chloride derivative of **6** in toluene at 90°C generated intractable mixtures of decomposition products, with significant recovery of unreacted **des-TMS-5**. It was reasoned that the poor nucleophilicity of the oxime ether, combined with elevated reaction temperatures, promoted decomposition of the diacid chloride before it could engage with the oxime. To remedy this, two modifications were implemented: (1) The TMS derivative **5** was prepared, inspired by the venerable Hosomi-Sakurai reaction[30] as it was envisaged that a β-silicon effect could enhance the nucleophilicity at nitrogen via σ(Si–C) to π donation.[31] (2) The reaction was conducted at lower temperature, using AgOTf to promote activation of the diacid chloride electrophile. Ultimately, this push-pull system of Si/Ag^+ activation delivered the condensation product **18** in moderate yield with surprising speed (reaction quenched after 7 minutes, see inset table 3 for selected optimization conditions). The reaction benefited from elevated temperature, although by-products became predominant above 50 °C. Acetonitrile proved to be the optimal solvent, and a methanol quench was employed to liberate product which had been acylated on the pyridone 4-OH by starting material. This enabled the facile recovery of the diacid fragment as a mixture of the mono- and di-methyl esters (25% + 22% respectively) which could be recycled to access additional **6**. A reasonable mechanistic proposal involves silver mediated activation of the diacid chloride derived from **6**, to produce a transient diacyl triflate, which is intercepted by oxime **5**, assisted by the appended TMS moiety. This would produce an enamine intermediate which could rapidly engage the second acyl electrophile in an intramolecular fashion to generate the pyridone ring. Additionally, TMSOTf generated *in situ* may serve to further enhance the reactivity of the electrophile (TMS derivatization is observed by LCMS). The importance of the silyl substituent on **5** is highlighted by the observation that **des-TMS-5** provides **18** in much lower yield (14%) under the same reaction conditions (see SI). This represents a unique pyridone synthesis and enables the construction of a remarkably hindered ring system, which exists as a mixture of interconverting atropisomers. Deprotection using TFA/MeOH afforded (–)-maximiscin **1** ($[\alpha]_D^{20.0} = -147$), completing a 10-step (LLS) total synthesis of this natural product (60% ideality).[32] All spectral data were wholly consistent with the original isolation report.[2]

Several unusual steps in this synthesis are worthy of note: (1) a scalable enantiocontrolled C–H activation-desymmetrization defined 4-stereocenters in a single step and enabled access to a highly-functionalized carbocycle from simple aromatic feedstock; (2) a radical disconnection, leveraging a Ag/Fe co-catalyzed stereoinvertive decarboxylative Giese addition, constructed a hindered C–C bond with concomitant radical translocation to a remote site; (3) a non-intuitive disconnection through the central hydroxypyridone ring enabled a highly convergent synthesis of **1** and led to the development of a new tactic to assemble such systems.

Scheme 1. Total synthesis of maximiscin (–)-**1**. [a]

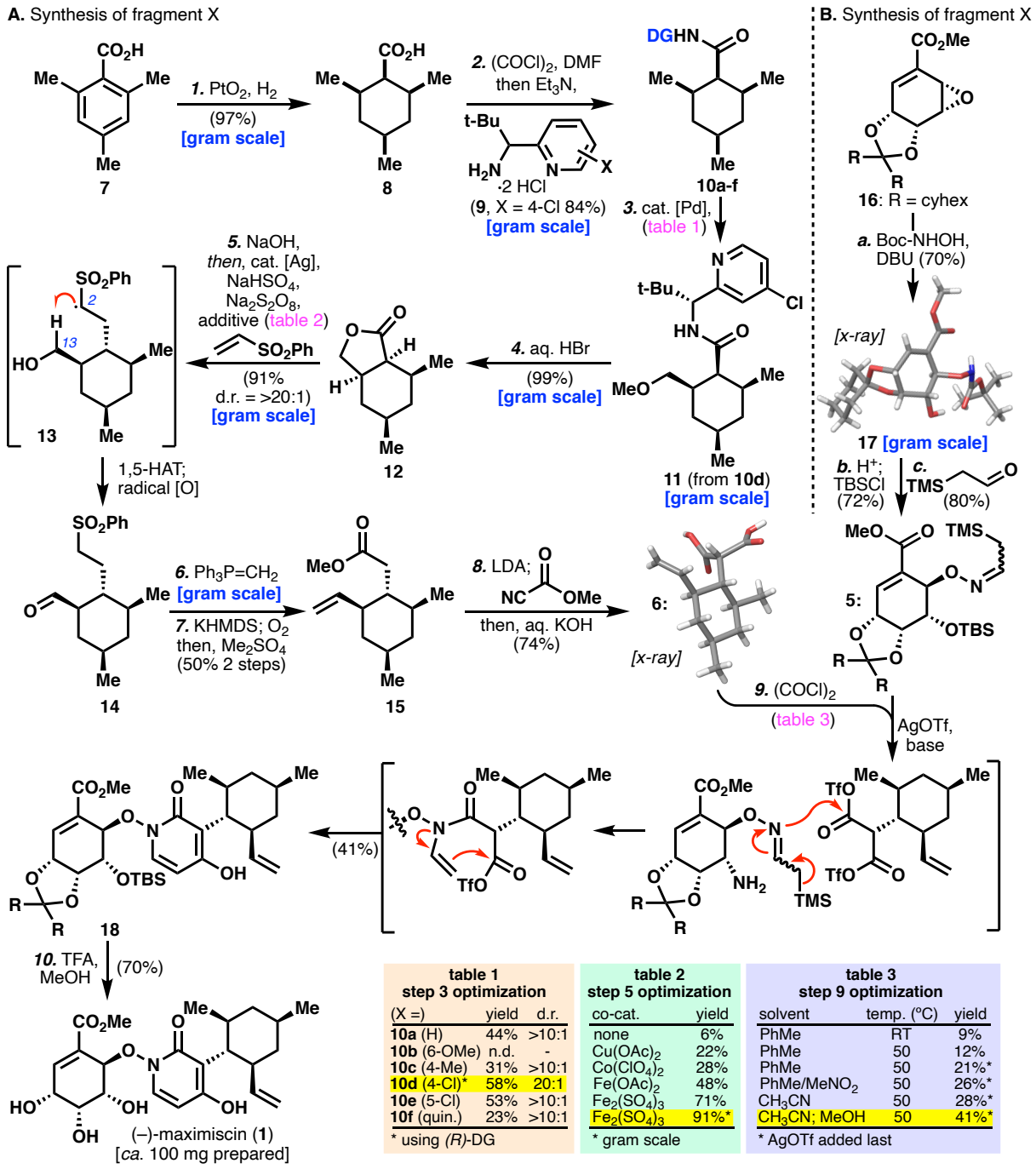

table 1
step 3 optimization

(X =)	yield	d.r.
10a (H)	44%	>10:1
10b (6-OMe)	n.d.	-
10c (4-Me)	31%	>10:1
10d (4-Cl)*	58%	20:1
10e (5-Cl)	53%	>10:1
10f (quin.)	23%	>10:1

* using *(R)*-DG

table 2
step 5 optimization

co-cat.	yield
none	6%
$Cu(OAc)_2$	22%
$Co(ClO_4)_2$	28%
$Fe(OAc)_2$	48%
$Fe_2(SO_4)_3$	71%
$Fe_2(SO_4)_3$	91%*

* gram scale

table 3
step 9 optimization

solvent	temp. (°C)	yield
PhMe	RT	9%
PhMe	50	12%
PhMe	50	21%*
PhMe/$MeNO_2$	50	26%*
CH_3CN	50	28%*
CH_3CN; MeOH	50	41%*

* AgOTf added last

[a]Reagents and conditions: (**1**). PtO_2 (5 mol%), H_2 (450 psi), AcOH, rt, 14 h. (**2**) $(COCl)_2$ (1.20 equiv), DMF (0.05 equiv), CH_2Cl_2, 0 °C to rt, 1 h, then **9** (1.00 equiv), Et_3N (3.70 equiv.), DMAP (0.05 equiv), PhMe, 70 °C, 2.5 h. (**3**) $Pd(OAc)_2$ (15 mol%), LiOAc (1.00 equiv), $NaIO_4$ (4.00 equiv), Ac_2O (2.00 equiv), PhMe/MeOH (2:1), 90 °C, 24 h. (**4**) aq. HBr, 100 °C, 15 h. (**5**) aq. NaOH (1.20 equiv), THF, MeOH, rt, 12 h, then $AgNO_3$ (30 mol%), $Fe_2(SO_4)_3$•$5H_2O$ (20 mol%), $NaHSO_4$•H_2O (1.13 equiv), $Na_2S_2O_8$ (2.50 equiv), phenyl vinyl sulfone (1.40 equiv), H_2O/CH_3CN (4:1), 40 °C, 3 h. (**6**) CH_3PPh_3Br (2.50 equiv), *n*-BuLi (2.30 equiv), THF, –5 °C to rt, 1 h. (**7**) KHMDS (2.50 equiv), O_2 (balloon), THF –78 °C to rt, 45 min, then Me_2SO_4 (3.50 equiv), rt, 1 h, then morpholine (3.00 equiv), rt, 30 min. (**8**) LDA (3.00 equiv), Et_2O, –78 °C to 0 °C, 1 h, then methyl cyanoformate (4.00 equiv), –78 °C, then methanol (excess), aq. KOH (8.20 equiv), EtOH, 80 °C, 12 h. (**9**) $(COCl)_2$ (2.50 equiv), DMF (0.08 equiv), CH_2Cl_2, rt, 2.5 h, then **5** (1.20 equiv), DTBMP (2.20 equiv), AgOTf (1.90 equiv), CH_3CN, 50 °C, 7 min. (**10**) TFA/MeOH (1:1), 0 °C to rt, 22 h. (**a**) *N*-Boc-NHOH (1.20 equiv), DBU (1.00 equiv), CH_2Cl_2, rt, 5 min. (**b**) TFA/CH_2Cl_2 (1:4), 0 °C, 15 min, then TBSCl (3.00 equiv), Imid. (4.00 equiv), DMAP (0.10 equiv), CH_2Cl_2, 12 h. (**c**) TMS-acetaldehyde (1.20 equiv), CH_2Cl_2, rt, 30 min. Abbreviations: DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene; DMAP = *N,N*-dimethyl-4-aminopyridine; DMF = N,N-dimethylformamide; DTBMP = 2,6-Di-tert-butyl-4-methylpyridine; imid. = imidazole; KHMDS = potassium bis(trimethylsilyl)amide; LDA = lithium diisopropylamide; TFA = trifluoroacetic acid; THF = tetrahydrofuran.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data (^{1}H and ^{13}C NMR, MS) for all new compounds as well as optimization tables. This material is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

E-mail: pbaran@scripps.edu (P.S.B.).

Notes

The authors declare no competing financial interest.

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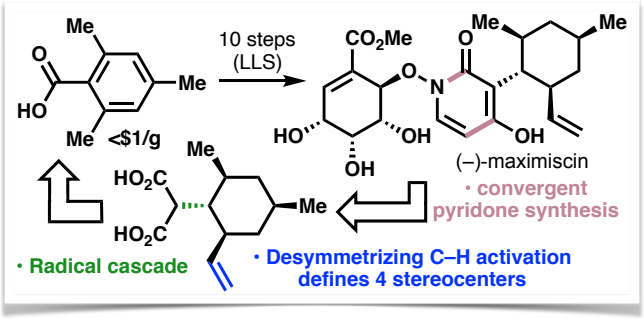
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• Desymmetrizing C–H activation
defines 4 stereocenters