Natural Products

International Edition: DOI: 10.1002/anie.201612447
German Edition: DOI: 10.1002/ange.201612447

Mccrearamycins A–D, Geldanamycin-Derived Cyclopentenone Macrolactams from an Eastern Kentucky Abandoned Coal Mine Microbe

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Abstract: *Four cyclopentenone-containing ansamycin polyketides (mccrearamycins A–D), and six new geldanamycins (Gdms B–G, including new linear and mycothiol conjugates), were characterized as metabolites of Streptomyces sp. AD-23-14 isolated from the Rock Creek underground coal mine acid drainage site. Biomimetic chemical conversion studies using both simple synthetic models and Gdm D confirmed that the mccrearamycin cyclopentenone derives from benzilic acid rearrangement of 19-hydroxy Gdm, and thereby provides a new synthetic derivatization strategy and implicates a potential unique biocatalyst in mccrearamycin cyclopentenone formation. In addition to standard Hsp90α binding and cell line cytotoxicity assays, this study also highlights the first assessment of Hsp90α modulators in a new axolotl embryo tail regeneration (ETR) assay as a potential new whole animal assay for Hsp90 modulator discovery.*

Geldanamycin (Gdm)-type polyketides are prototypical microbial benzoquinone ansamycin anticancer agents that target the N-terminal ATP-binding domain of heat shock protein 90 (Hsp90; Figure 1 A).[1] While a number of elegant and efficient Gdm synthetic and biosynthetic production and derivatization strategies have been developed,[2] C-17 semi-synthetic Gdm modification was a key to both first (tanespimycin/17-AAG[3] and orally bioavailable alvespimicin/17-DMAG)[4] and second (retaspimycin hydrochloride/IPI-

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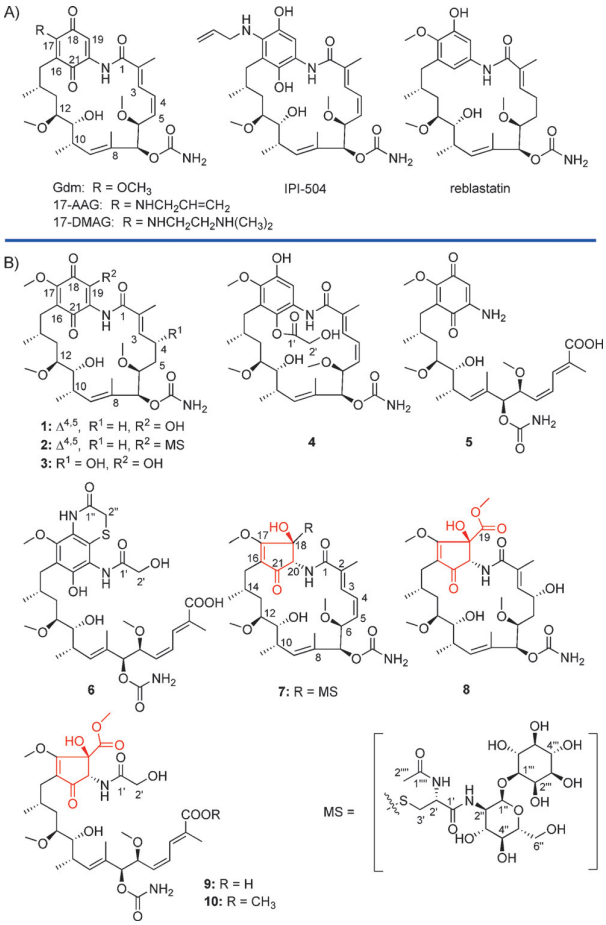
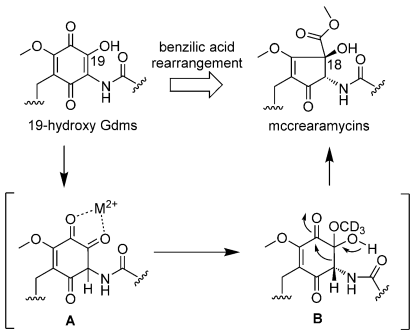


Figure 1. A) Chemical structures of representative Gdm-type ansamycins and B) new compounds isolated from *Streptomyces* sp. AD-23-14. The unique cyclopentenone ring structure of mccrearamycins A–D is highlighted in red.

504)[5] generation analogues advanced to the clinic (Figure 1 A), the latter of which displayed improved solubility and reduced hepatotoxicity.[6] More recent medicinal chemistry efforts have focused on C-19 substitution to prohibit non-specific alkylation (a putative contributor to non-selective toxicity), analogues of which were found to opportunistically favor the *cis*-amide conformer observed in the Gdm-Hsp90 ligand-bound complex.[7] As part of a microbial natural products discovery effort from coal-mining-associated environments in Kentucky, USA,[8] herein we describe the isolation and structure elucidation of six new Gdm analogues (**1**–**6**), and four unprecedented ring-contracted cyclopentenone macrolactams (mccrearamycins A–D, **7**–**10**) from the Rock Creek (McCreary County) underground coal mine acid drainage isolate *Streptomyces* sp. AD-23-14 (Figure 1 B). Biomimetic studies using both simple synthetic models and isolated Gdm analogues revealed the *ortho*-quinone to undergo a facile benzilic acid rearrangement to provide the ring-contracted cyclopentenone scaffold, presenting both a new synthetic strategy and implicating the role of a potential novel biocatalyst for ansamycin ring contraction. In addition to expanding Hsp90α inhibitor SAR, these studies also highlight the first assessment of Hsp90α modulators in a new axolotl (*Ambystoma mexicanum*) embryo tail regeneration (ETR) assay.[9]

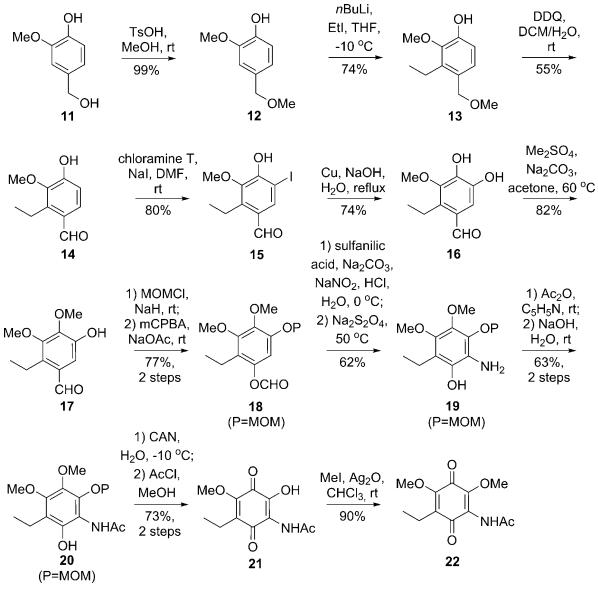
Gdms B–G (**1**–**6**) were characterized as new Gdm analogues (including mycothiol conjugate **2** and linear Gdms **5**–**6**) based on NMR, MS, and comparison with literature precedent (see Figure 1 and the Supporting Information). While **7**–**10** also shared the signature spectral features of Gdm 19-membered macrolactams (Figures S2–S4), they notably lacked indicators of the corresponding Gdm 1,4-benzoquinone. Key HMBC correlations [for example, for **7**, from a nitrogen-bearing CH ($\delta_H = 5.12$ ppm, 20-H) to C-16 ($\delta_C =$ 116.2 ppm), C-17 ($\delta_C = 177.0$ ppm) and C-18 ($\delta_C = 71.1$ ppm), and from 18-OH ($\delta_H = 6.16$ ppm) to C-17 and C-18] implicated an unprecedented alternative cyclopentenone ring (Figure 1 B) in **7**–**10**. Determination of C-18 substitution (MSH in **7**; methyl formate in **8**–**10**) relied on HMBC correlations (Figures S2 and S3). The relative configurations of **7**–**10** were established through NOESY (Figures S3 and S4) where many observed modifications paralleled those of corresponding Gdm analogues. Namely, like **3** (Gdm D), hydration of the **8** C-4/C-5 double bond was observed, and similar to **6** (Gdm G), **9** and **10** were also identified as N-20-acyl (2-hydroxy-acetate) linear metabolites (Tables S1 and S4, Figures S2–S4). These cumulative analyses established **7**–**10** as new ring-contracted cyclopentenone macrolactams and thus were named mccrearamycins A–D in reference to the structural novelty and the producing strain's point of origin.

The similarities between Gdms and mccrearamycins from *Streptomyces* sp. AD-23-14 implicated Gdms as potential mccrearamycin progenitors (Scheme 1). In addition, while NOESY firmly established the cyclopentenone C-18/C-20 relative *trans*-configuration in **7**, the key ^{1}H NMR resonance for 18-OH was lacking for **8**–**10**. For further validation, a model study was pursued to assess cyclopentenone formation via ring contraction of a 19-OH Gdm progenitor (Scheme 1) reminiscent of the classical cyclohexanone to



Scheme 1. Proposed metal (M^{2+})-mediated benzilic acid rearrangement of the Gdm hydroxyquinone to afford the mccrearamycin cyclopentenone.

cyclopentane-1-carboxylate benzilic acid rearrangement.[10] While the corresponding Gdm rearrangement is unprecedented, the analogous Hooker oxidation rearrangement of hydroxynaphthoquinones to indane carboxylic acids served as related precedent.[11] For this study, the synthesis of the Gdm model surrogate 2-hydroxyquinone **21** (Scheme 2) commenced with aryl lithiation–alkylation of benzyl methyl ether **12**. DDQ-mediated oxidation of **13** followed by hydroxy-directed iodination provided phenol **15**. The iodide was then treated with copper powder in basic medium to provide catechol **16**, which was selectively methylated by Me_2SO_4. Methoxymethyl protection of the remaining phenolic hydroxyl followed by Baeyer–Villiger oxidation produced the key intermediate **18**. Consistent with challenges associated with hexasubstituted benzene syntheses,[12] amination, amidation, and nitration of **18** directly, or of corresponding halogenated derivatives using transition-metal catalysts, failed to give desired aniline **19** or amide **20**. However, azo coupling with sulfanilic acid,[13] followed by dithionite reduc-



Scheme 2. Synthesis of templates **21** and **22.**

tion, gave aniline **19** in 62% yield. Sequential acetylation, hydrolysis, oxidation, and deprotection furnished template **21** in 73% yield, and methylation of **21** further afforded the corresponding 2-methoxy quinone **22** as an additional comparator.

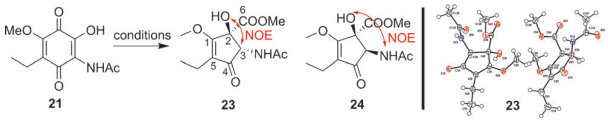
Consistent with the impact of $CuCl_2$ on benzilic acid rearrangement stereoselectivity and yield,[14] evaluation of the putative **21** benzilic acid rearrangement in the presence of transition metal salts and various other known benzilic acid rearrangement promoters revealed $CoCl_2$ to afford the best overall yield and stereoselectivity (Table 1). Single-crystal X-ray diffraction of the isolated product **23** further established the relative C-2/C-3 *trans*-configuration (Table 1 and S7, CCDC 1496415), consistent with the signature **23** 2-OH to 3-CH NOE and corresponding 18-OH to 20-CH NOE of mccrearamycin A (**7**). A putative mechanism for Co^{2+}-assisted benzilic acid rearrangement is depicted in Scheme 1. Consistent with this mechanism, the substitution of CH_3OH with CD_3OD as solvent led to selective isotopic label incorporation in **25** (entry 18, Table 1). Importantly, the 2-methoxy model **22** and the prototypical Hooker reaction substrate lawsone failed to give the desired benzilic acid rearrangement under the optimized conditions (Scheme S1).

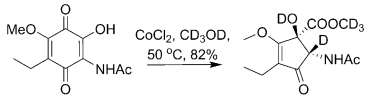
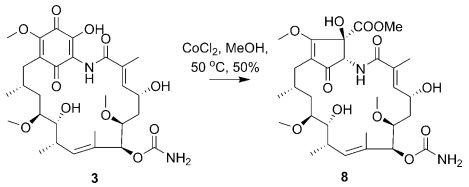
To probe the relevance to mccrearamycins, this biomimetic model study was subsequently extended to the corresponding 19-hydroxy-substituted Gdm D (**3**). Remarkably, reaction of **3** under the same optimized conditions led to 50% conversion to mccrearamycin B (**8**; entry 19, Table 1 and Figures S6–S8). The established stereoselectivity of the model reaction implicates an **8** cyclopentenone C-18/C-20 *trans*-configuration identical to that of **7** and **23**. Comparison of select ^{13}C NMR chemical shifts in mccrearamycins B–D (**8**–**10**) to that of the *trans*- and *cis*-configured models (**23** and **24**, respectively) provide further support of a common benzilic acid rearrangement-derived C-18/C-20 *trans*-configuration in all of the mccrearamycins (Table S5). Subsequent indirect mccrearamycin absolute configuration assignment was accomplished through electronic circular dichroism (ECD) analysis. Specifically, comparison of the ECD spectra of **8** in MeOH to the theoretical ECD spectra [generated using time-dependent density functional theory (TDDFT)][8a,15] for two possible isomers of **8** (**8a**: 4*R*, 6*S*, 7*S*, 10*S*, 11*R*, 12*S*, 14*R*, 18*S*, 20*S* and **8b**: 4*R*, 6*S*, 7*S*, 10*S*, 11*R*, 12*S*, 14*R*, 18*R*, 20*R*), revealed that of **8a** as providing the best spectral match (Figure S9).

Based on the established mechanism of Gdm and related analogues, all of the isolated compounds were evaluated in standard Hsp90α inhibition[8b] and cancer cell line (human non-small cell lung A549) cytotoxicity assays (Table S7). This cumulative analysis revealed the parental prototypes (Gdm, reblastatin, and 17-*O*-demethyl-reblastatin) to afford greatest Hsp90α inhibition (IC_{50}s of 5–30 nM) with notably divergent corresponding cytotoxicities (Gdm IC_{50} 1 nM, reblastatin IC_{50} 0.7 μM, and 17-*O*-demethyl-reblastatin $IC_{50} > 50$ μM), suggesting the oxidation state and substitution pattern contribute to differences in cellular uptake and/or alternative cytotoxicity mechanisms consistent with prior Gdm SAR studies.[7a,16] Similar to that of the parental prototypes, the corresponding cytotoxicity of the new *Streptomyces* sp. AD-23-14 metabolites did not correlate with Hsp90α inhibitory potential in some cases.

Streptomyces sp. AD-23-14 metabolites were also evaluated using a highly regenerative salamander model, the Mexican axolotl (*Ambystoma mexicanum*).[17] Previous transcriptional studies found *hsp90aa1* to be significantly upregulated 12 hours after axolotl limb and tail amputation, suggesting a role for Hsp90 in tissue regeneration.[9] To investigate this further, we used the axolotl embryo tail regeneration (ETR) assay[9b] to test Gdm for an inhibitory effect on tail regeneration. Tail-amputated axolotl embryos were incubated in microtiter plates in the absence (vehicle control, DMSO) or presence of 10 μM agent (Gdm, reblastatin, 7-*O*-demethyl-reblastatin, and **1**–**10**) and imaged on day 1 (pre-treatment) and day 7. An initial single dose screen revealed Gdm to completely inhibit tail regeneration with no

Table 1: Optimization of benzilic acid rearrangement and biomimetic conversion of **3** to **8**.



Entry[a]	Additives	Temp. [°C]	Solvent	Time [h]	Ratio[b] (**23**/**24**)	Yield[c] of **23**
1	none	50	$MeOH/CH_2Cl_2$	16	–[d]	
2	KOtBu	50	$MeOH/CH_2Cl_2$	16	–[d]	
3	DBU	50	$MeOH/CH_2Cl_2$	16	2:1	51%
4	TEA	50	$MeOH/CH_2Cl_2$	16	5:1	60%
5	DABCO	50	$MeOH/CH_2Cl_2$	16	1:1	
6	DIPEA	50	$MeOH/CH_2Cl_2$	16	4:1	55%
7	$CoCl_2$	50	$MeOH/CH_2Cl_2$	16	>10:1	73%
8	$NiCl_2$	50	$MeOH/CH_2Cl_2$	16	–[e]	
9	$CuCl_2$	50	$MeOH/CH_2Cl_2$	16	–[e]	
10	AgOTf	50	$MeOH/CH_2Cl_2$	16	1:5	39%[f]
11	$Au(PPh_3)Cl$	50	$MeOH/CH_2Cl_2$	16	–[d]	
12	$Co(OAc)_2$	50	$MeOH/CH_2Cl_2$	16	ND[g]	24%
13	$Co(acac)_2$	50	$MeOH/CH_2Cl_2$	16	ND[g]	15%
14	$CoCl_2$	50	$MeOH/CHCl_3$	16	ND[g]	29%
15	$CoCl_2$	50	MeOH/DCE	16	>10:1	31%
16	$CoCl_2$	50	MeOH	40	>10:1	82%
17	$CoCl_2$	80	MeOH	16	>10:1	85%
18						
19						

[a] Reactions contained substrate (0.05 mmol) and additives (0.1 mmol) in 0.5 mL solvent under specified conditions with product formation subsequently assessed by analytical HPLC and NMR (key NOE signatures are highlighted, see the Supporting Information for experimental details). [b] Based on analytical HPLC peak integration. [c] Yields of isolated products. [d] No reaction. [e] Undefined mixture. [f] Yield of isolated product **24**. [g] Not determined.

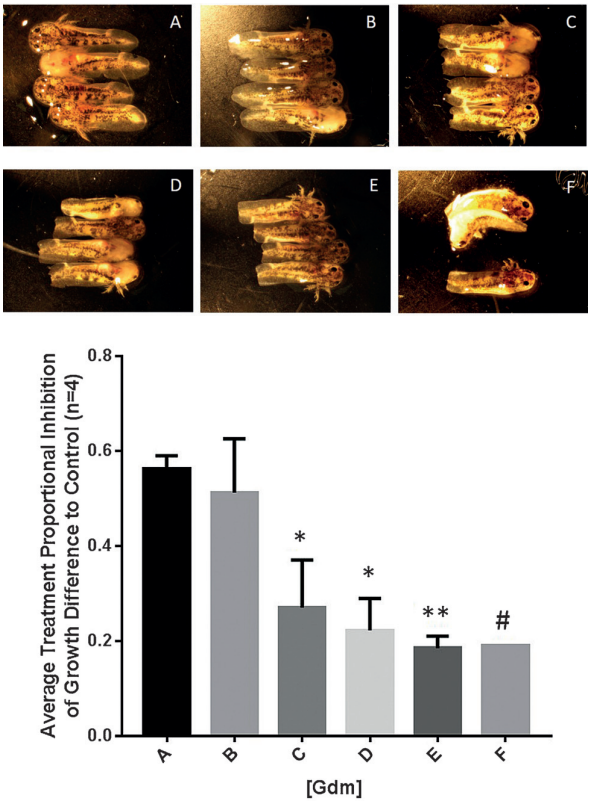


Figure 2. The impact of [Gdm] on axolotl embryo tail regeneration as determined by the ETR assay (*$p < 0.005$, **$p < 0.0001$, $n = 4$; #: 3 axolotls were dead at day 7; A: DMSO control; B: 0.1 μM; C: 1 μM; D: 2.5 μM; E: 5 μM; F: 10 μM).

effect observed for all of the other test agents. Subsequent studies revealed a clear dose-response for Gdm, with developmental abnormalities and toxicity observed at the highest dose (10 μM), inhibition of regeneration at intermediate doses, and no effect on regeneration at the lowest dose (0.1 μM; Figure 2).

In summary, metabolic profiling led to the discovery of new Gdm analogues and a set of cyclopentenone macrolactams. The development and implementation of a cobalt-mediated benzilic acid rearrangement served as a key feature in mccrearamycin structure validation and highlights the potential synthetic utility in the context of 2-hydroxyquinone-containing complex natural products. That cyclopentenone formation requires distinct conditions may also implicate a unique biosynthetic pathway. These metabolites, together with the parental prototypes, also served as a test set to assess the impact of Hsp90 inhibitors in vivo using an axolotl ETR assay. While developmental abnormalities have been observed in many organisms (including zebrafish administered Gdm[18]) when Hsp90 activity is reduced below critical levels,[19] our results demonstrate that Gdm can be administered at a dose that blocks regeneration without overtly affecting development. This study implicates Gdm as a useful reagent to probe the role of Hsp90 in axolotl tail regeneration and suggests low dose Gdm could be used in a sensitized, ETR chemical genetic screen to identify new Hsp90 modulators.

Acknowledgments

This work was supported by National Institutes of Health grants R24 OD21479 (SRV, JST), T32 DA016176 (YZ), the University of Kentucky College of Pharmacy, the University of Kentucky Markey Cancer Center, and the National Center for Advancing Translational Sciences (UL1TR001998).

Conflict of interest

J.S.T. is a co-founder of Centrose (Madison, WI).

Keywords: ansamycin · axolotl · biomimetic synthesis · Hsp90 · regeneration

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 2994–2998
Angew. Chem. **2017**, *129*, 3040–3044

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Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.

Manuscript received: December 22, 2016
Revised: January 18, 2017
Final Article published: February 1, 2017

