Natural Product Synthesis

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Total Synthesis of (+)-Rugulosin and (+)-2,2′-*epi*-Cytoskyrin A through Cascade Reactions**

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We have previously reported[1] the development of the "cytoskyrin cascade" as a facile and efficient entry into the growing class of modified bisanthraquinones that includes cytoskyrin A (**1a**),[2] graciliformin (**1b**),[3] and rugulosin (**2b**; Figure 1).[1c,4] Isolated from a number of fungi and lichens,[4b]

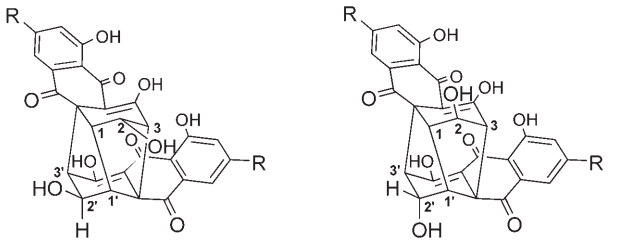

Figure 1. Selected naturally occurring modified bisanthraquinones.

the latter compound (**2b**) was recently found to exhibit anti-HIV properties,[5] in addition to its originally reported cytotoxic activity[4b] that it shares with cytoskyrin A (**1a**).[2] Given the occurrence of both graciliformin (**1b**) and rugulosin (**2b**) in nature, it will not be surprising if 2,2′-*epi*-cytoskyrin A (**2a**) is someday discovered as a natural product, for its structural relationship to cytoskyrin A (**1a**) is the same as that of **2b** to **1b**. The multistep "cytoskyrin cascade" was demonstrated on a model system that differed from the

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natural products by the absence of a hydroxy group at the C2 and C2′ positions (see Figure 1). The presence of these hydroxy groups was considered to be problematic for a total synthesis involving dimerization of two monomeric units, as their elimination was anticipated to be favored by aromatization, and hence facile. Although nature is probably carrying out this dimerization process with a hydroxy group in place, a recent report[1b] confirmed that attempts to synthesize the monomeric anthradihydroquinone featuring a benzyl-protected hydroxy group at the C2 and C2′ positions resulted in elimination of benzyl alcohol. Herein, we report the first biomimetic, asymmetric total synthesis of (+)-2,2′-*epi*-cytoskyrin A (**2a**) and (+)-rugulosin (**2b**) through the "cytoskyrin cascade", under conditions that successfully overcome the above-mentioned challenges.

There are four possible spatial arrangements (**A**–**D**) for the dimerization of the monomeric anthraquinones, two *endo* (**A**, **B**) and two *exo* (**C**, **D**) arrangements, which are further distinguished by the faciality of approach, the one from the top (**B**, **D**) and the one from below (**A**, **C**), as demonstrated in Figure 2. The two *endo* alignments (**A** and **B**) are equivalent and are unlikely, if not impossible, due to structural constraints. The *exo-syn* arrangement (**C**) would place the two substituted hydroxy groups (OR^1) in a *syn* arrangement resulting in the build-up of significant steric congestion and should, therefore, be disfavored. A pathway through such an arrangement would form *ent*-cytoskyrin (*ent*-**1a**) and *ent*-graciliformin (*ent*-**1b**) through the intermediacy of *O*-bridged dimers **3**. The alternative *exo-anti* arrangement (**D**), places these two interfering groups opposite to each other, hence minimizing the steric congestion and allowing the generation of 2,2′-*epi*-cytoskyrin A (**2a**) and rugulosin (**2b**). It is interesting to note that while the chirality of the monomeric anthraquinone is responsible for determining the absolute configuration of the cage, the diastereoselectivity of the dimerization step controls the relative stereochemistry of the C2 and C2′ centers relative to the rest (epimeric stereochemistry) in the final product of the cascade sequence (see also caption, Figure 2).

Reasoning that the nature of the groups (R^1) residing on the C2/C2′ hydroxy groups may make a difference in the outcome of the anticipated reactions, we proceeded to construct different monomeric units as starting materials for the cascade. Scheme 1 summarizes the synthesis of hydroquinones **11a**–**11c** featuring a Hauser annulation[6] to construct the requisite tricyclic system. Thus, protection of the known diacetate **5**[7] with MOMCl or TBSCl followed by desymmetrization using porcine liver esterase (PLE) at pH 8 afforded alcohols **6a**[8] or **6b**[7] in 95 and 90% yield, respectively, over the two steps. PCC oxidation under buffered conditions using NaOAc followed by brief (10 min) exposure to DBU at 25 °C furnished the desired enones **7a** or **7b** in 68 and 67% yield, respectively, over the two steps. The other partners for the Hauser annulation, nitriles **10a** and **10b** were synthesized as shown in Scheme 1. Thus, protection of the commercially available salicylic acids **8a** or **8b** with excess TBSCl followed by treatment with $(COCl)_2$ and a catalytic amount of DMF in CH_2Cl_2 at 0 °C afforded the corresponding acid chlorides, which were quenched with Me_2NH to furnish

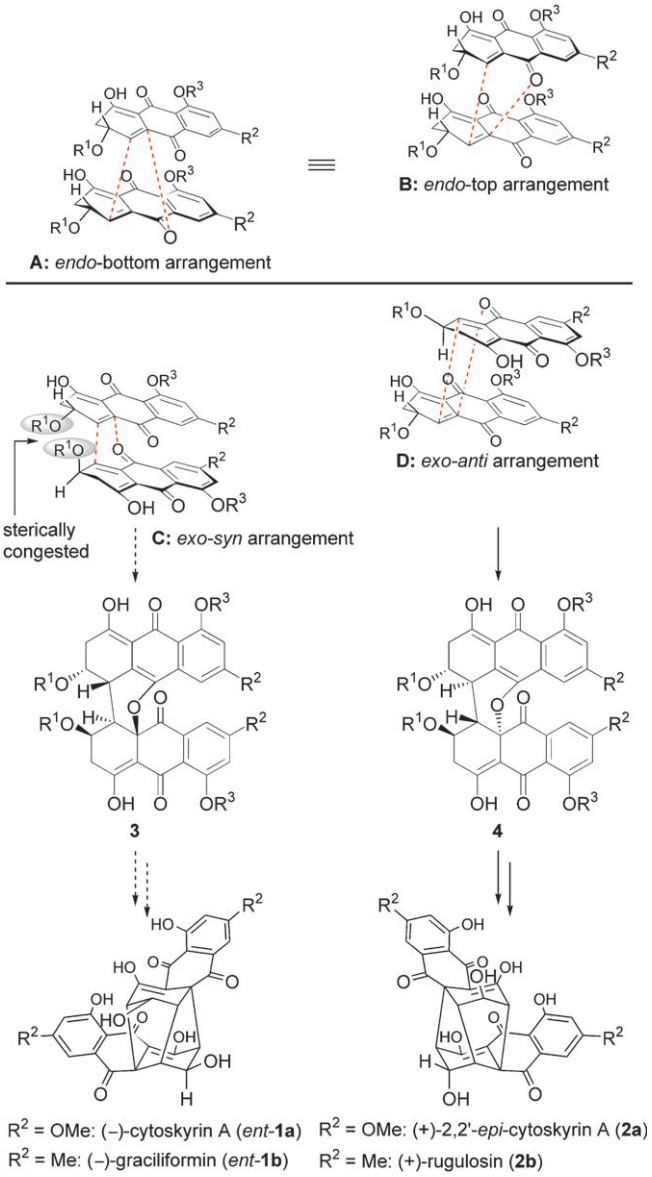
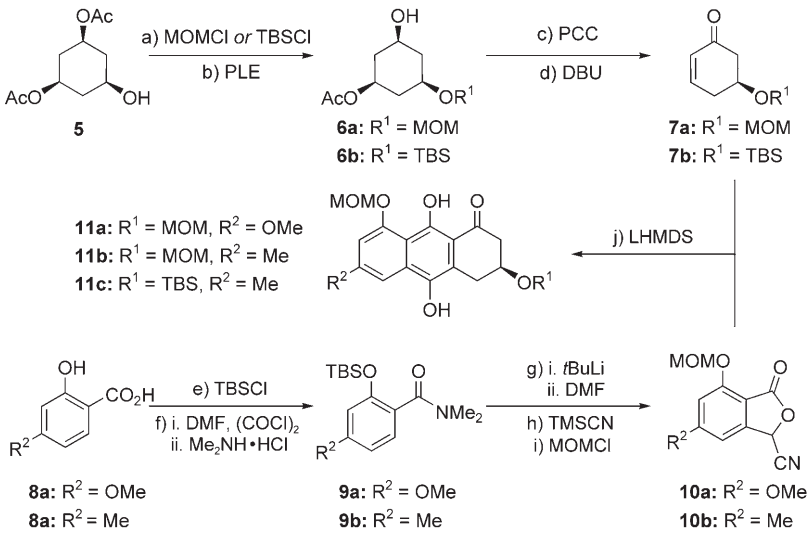


Figure 2. Stereoselectivity considerations for the dimerization step of anthradihydroquinones to modified bisanthraquinones. The shown enantiomers of the starting anthraquinones correspond to *ent*-**1a**, *ent*-**1b**, **2a**, and **2b**. Should the pathway involving arrangement **C** be possible, the opposite enantiomers would have been needed to obtain natural cytoskyrin A (**1a**) and graciliformin (**1b**).

amides **9a** or **9b** in 85 and 74% yield, respectively, over the three steps. *Ortho*-lithiation of amides **9a** or **9b** using *t*BuLi and TMEDA at −78 °C and subsequent quenching with freshly distilled DMF yielded the corresponding aldehydes. Exposure of the latter compounds to TMSCN, a catalytic amount of KCN, [18]crown-6, and AcOH afforded the deprotected nitrile compounds, which were finally treated with MOMCl and iPr_2NEt at 0 °C to furnish the required building blocks **10a** and **10b** in 64 and 50% yield, respectively, over the three steps.

With the two fragments in hand, the stage was now set for the synthesis of the requisite anthradihydroquinones **11a**–**11c**. Treatment of nitriles **10a** or **10b** with LHMDS in THF at

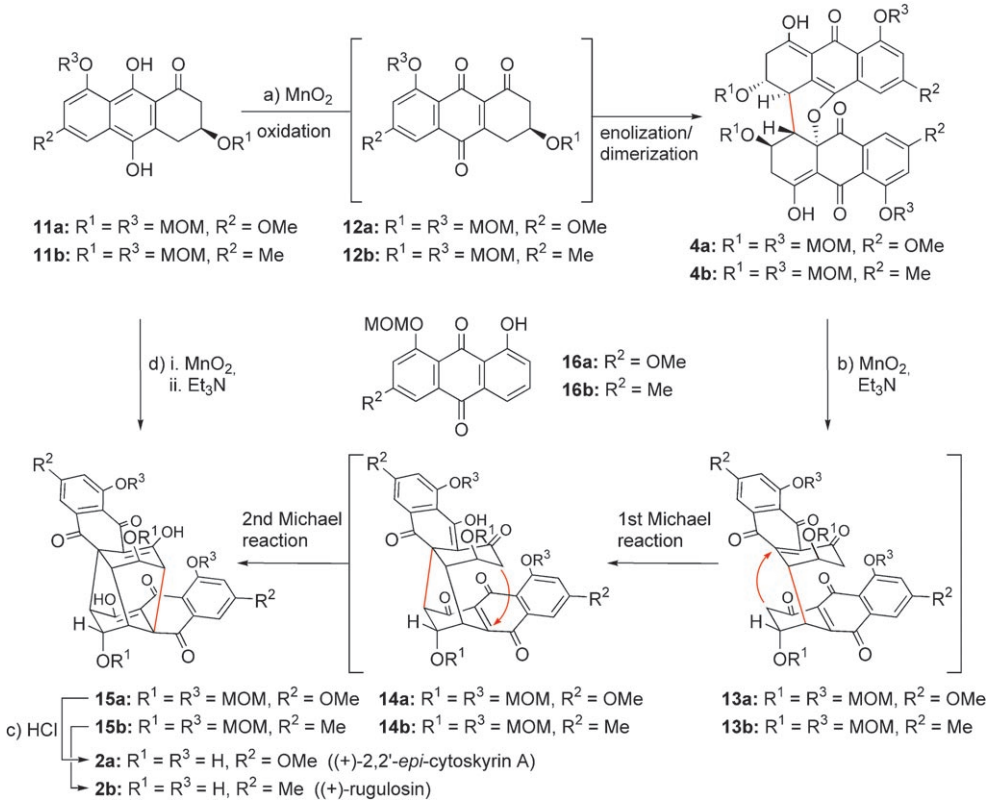


Scheme 1. Reagents and conditions: a) MOMCl (3.8 equiv), *i*Pr_2NEt (3.8 equiv), CH_2Cl_2, 25 °C, 1.5 h; TBSCl (3.8 equiv), imid (3.8 equiv), CH_2Cl_2, 25 °C, 48 h; b) PLE (1.0 equiv), buffer pH 8 (0.1 M), *t*BuOH (8% v/v), 25 °C, 4 h, 95% (**6a**), 90% (**6b**) over two steps;[8] c) PCC (3.0 equiv), NaOAc (3.0 equiv), CH_2Cl_2, 25 °C, 12 h; d) DBU (1.0 equiv), CH_2Cl_2, 25 °C, 10 min, 68% (**7a**), 67% (**7b**) over two steps; e) TBSCl (4.0 equiv), imid (6.0 equiv), DMF, 25 °C, 16 h; f) i. $(COCl)_2$ (1.25 equiv), DMF (cat.), CH_2Cl_2, 0 °C, 2 h; ii. $Me_2NH{\cdot}HCl$ (1.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 0 °C, 30 min, 85% (**9a**), 74% (**9b**) over three steps; g) TMEDA (3.0 equiv), *t*BuLi (3.0 equiv), DMF (3.0 equiv), THF, −78→25 °C, 12 h; h) KCN (0.2 equiv), [18]crown-6 (0.2 equiv), TMSCN (1.4 equiv), CH_2Cl_2, 25 °C, 4 h; then AcOH, 12 h; i) MOMCl (1.5 equiv), *i*Pr_2NEt (1.2 equiv), CH_2Cl_2, 0 °C, 1 h, 64% (**10a**), 50% (**10b**) over three steps; j) **10** (1.1 equiv), THF, LHMDS (1.1 equiv), −78 °C; then **7** (1.0 equiv), −78→0 °C, 2 h, (submitted directly to the cascade). MOM = methoxymethyl; TBS = *tert*-butyldimethylsilyl; PLE = porcine liver esterase; PCC = pyridinium chlorochromate; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF = *N*,*N*′-dimethylformamide; TMEDA = tetramethylethylenediamine; THF = tetrahydrofuran; TMS = trimethylsilyl; LHMDS = lithium bis(trimethylsilyl)amide.

−78 °C, followed by addition of **7a** or **7b** (−78→0 °C) gave crude anthradihydroquinones **11a**–**11c**, which were directly subjected to the cytoskyrin cascade[1a] (Scheme 2). We had already established the facilitating role[1a] of MnO_2 and anticipated that the mild reaction conditions employed for the cascade coupled with the expected reluctance of the final compound to lose its alkoxy groups by virtue of Bredt's rule[9] would enable arrival at compounds **2a** and **2b**, provided that the feared elimination/aromatization pathway from the monomeric anthraquinones did not predominate. Indeed, exposure of **11a** or **11b** to MnO_2 (1.5 wt equiv) in a concentrated CH_2Cl_2 solution (0.35 M) at 25 °C for 30 min resulted in the formation of dimeric compounds **4a** or **4b** as single diastereoisomers in 64 and 32% yield, respectively, through a sequence featuring oxidation to the corresponding anthraquinone (**12a** or **12b**) and dimerization of its easily generated, under the reaction conditions, enol form. It was found that when crude **11a** or **11b** were used, the cascade was shutdown at the stage of **4a** or **4b**. This occurrence was attributed to an, as yet unknown, impurity[10] carried through from the Hauser annulation which hindered the oxidation of **4a** or **4b** to **13a** or **13b**, impeding the cascade. Prolonged exposure of the thus-obtained **4a** or **4b** to MnO_2 (12 h) resulted in quantitative formation of **16a** or **16b**, presumably through two successive retro-Michael reactions (see Scheme 3) followed by elimination and aromatization. However, treatment of purified **4a** or **4b** (flash column chromatography on silica gel) with MnO_2 (1.5 wt equiv) and Et_3N (5.0 equiv, added as soon as **14a** or **14b** were observed by thin layer chromatography (TLC), ca. 6 h) in CH_2Cl_2 at 45 °C for 12 h resulted in the formation of **15a** or **15b** in 71 and 81% yield, respectively, through the intermediacy of fleeting compounds **13a** or **13b** and **14a** or **14b**.

Use of carefully purified **11a** or **11b** (preparative TLC) enabled the realization of an impressive seven-step cascade sequence featuring the transformation of tricyclic monomers **11a** or **11b** into nonacyclic systems **15a** or **15b** in 60 and 50% yield, respectively, involving a sequence of alternating oxidations and double Michael reactions as shown in Scheme 2. The remaining mass was accounted for by the formation of aromatized monomers **16a** or **16b** in 40 and 50% yield, respectively. This cascade required treatment of **11a** or **11b** with MnO_2 (1.5 wt equiv) in CH_2Cl_2 (0.35 M) for 10 min at 25 °C, conditions that led to the formation of **4a** or **4b** as indicated by TLC, followed by tenfold dilution with CH_2Cl_2 and addition of a further 1.5 wt equiv of MnO_2 until the formation of **14a** or **14b** was complete (6 h). Finally, addition of Et_3N (5.0 equiv) and heating to 45 °C for 6 h furnished **15a** or **15b**. Exposure of the latter compounds (**15b** or **15b**) to concentrated HCl in a mixture of MeOH and THF (20:1) resulted in global deprotection, affording (+)-2,2′-*epi*-cytoskyrin A (**2a**) or (+)-rugulosin (**2b**) in 93 and 98% yield, respectively. The ^{1}H NMR spectrum of (+)-rugulosin (**2b**) in [D_6]DMSO was identical to that reported in the literature[4c] for the naturally occurring substance. Besides being anticipated on the basis of the above arguments (Figure 2), the stereochemistry of **2a** was firmly established through spectroscopic analysis. Thus, the ^{1}H NMR spectrum of synthetic (+)-2,2′-*epi*-cytoskyrin A (**2a**) exhibited doublets for H3/H3′ ($\delta = 2.85$, $J = 4.8$ Hz) and H2/H2′ ($\delta = 4.49$, $J = 4.8$ Hz), while in the spectrum reported for naturally occurring cytoskyrin A (**1a**)[2] both signals for H3/H3′ ($\delta = 2.85$) and H2/H2′ ($\delta =$ 4.00) appear as singlets. If **2a** was to have the same stereochemistry as cytoskyrin (**1a**) at C2/C2′, the dihedral angle of H1/H1′-H2/H2′ and H2/H2′-H3/H3′ would have been 78° and 85°, respectively (manual molecular models)[3] and hence the signals for H3/H3′ and H2/H2′ would have been singlets. Crystals of synthetic rugulosin (**2b**) obtained by slow crystallization from acetone containing 1% Et_3N over MeOH vapors yielded to X-ray crystallographic analysis (see ORTEP drawing,[11] Figure 3), proving unambiguously its structure and, indirectly, rendering further support for the assigned structure of (+)-2,2′-*epi*-cytoskyrin A due to the striking closeness of the ^{1}H NMR spectra of **2a** and **2b**.

Having established a viable pathway to 2,2′-*epi*-cytoskyrin A (**2a**) and rugulosin (**2b**) starting from **11a** or **11b**,



Scheme 2. The cytoskyrin cascade: synthesis of (+)-2,2′-*epi*-cytoskyrin A (**2a**) and (+)-rugulosin (**2b**) from anthradihydroquinone **11a** or **11b**, respectively. Reagents and conditions: a) MnO_2 (1.5 wt equiv), CH_2Cl_2 (0.35 M), 25 °C, 1 h, 64% (**4a**), 32% (**4b**) over five steps; b) MnO_2, (1.5 wt equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25→45 °C, 12 h, 71% (**15a**), 81% (**15b**) over three steps; c) conc. HCl, MeOH, THF, 60 °C, 12 h, 93% (**2a**), 98% (**2b**); d) MnO_2 (1.5 wt equiv), CH_2Cl_2, 25 °C, 10 min; then MnO_2 (1.5 wt equiv), Et_3N (5.0 equiv), 25→45 °C, 12 h, 60% (**15a**), 40% (**16a**), 50% (**15b**), 50% (**16b**).

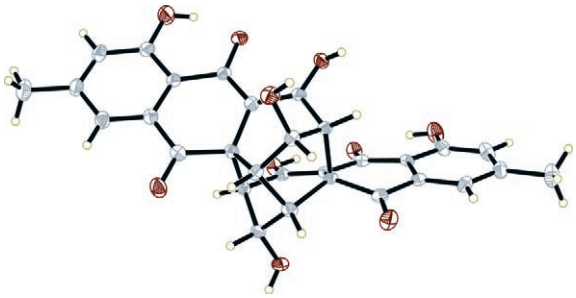


Figure 3. ORTEP drawing of rugulosin (**2b**) derived from X-ray crystallographic studies (O burgundy, C gray, H yellow). The molecule of Et_3N per molecule of **2b** is not shown. The crystallographic analysis did not reveal the absolute stereochemistry of **2b**, which was assigned as shown, on the basis of the absolute stereochemistry of the starting material and its positive optical rotation.[1c,4]

respectively, we then proceeded to investigate TBS-anthradihydroquinone **11c** as a substrate for the cytoskyrin cascade. It was reasoned that the sheer bulk of the TBS group as compared to the smaller MOM moiety was expected to retard both Michael reactions, an occurrence that could result in the isolation of some of the postulated intermediates of the cascade. Scheme 3 summarizes our findings, which indeed included the isolation of two of the reactive species involved, quinone **12c** and highly labile dimer **18**, both of which were characterized by ^{1}H NMR spectroscopy (see Table 1). Thus treatment of **11c** with MnO_2 (1.5 wt equiv) in a concentrated CH_2Cl_2 solution (0.35 M) at 25 °C for 30 min resulted in the slow formation of quinone **12c**, dimer **18**, product **4c**, and aromatized system **16b**. Moreover, compound **18**, upon standing in $CDCl_3$, slowly and quantitatively converted into **4c** and **16b** (**4c**/**16b** ≈ 1:3, as determined by ^{1}H NMR spectroscopy). This suggests that compounds **12c**, **17**, and **18** are in equilibrium with each other and that the rate of aromatization of **17** to **16b** is faster than the second Michael reaction within dimer **18** that leads to the desired compound **4c**. These observations were consistent with a stepwise mechanism for the cytoskyrin cascade involving two consecutive Michael reactions as shown in Figure 3, at least in the case of the TBS-protected derivative **11c**.

The described chemistry demonstrates the power of cascade reactions in chemical synthesis[12] and underscores the applicability of such processes in situations facing seemingly intransigent synthetic challenges. Further applications of these remarkable cascade reactions to the synthesis of other natural and designed members of the bisanthraquinone class should be forthcoming.

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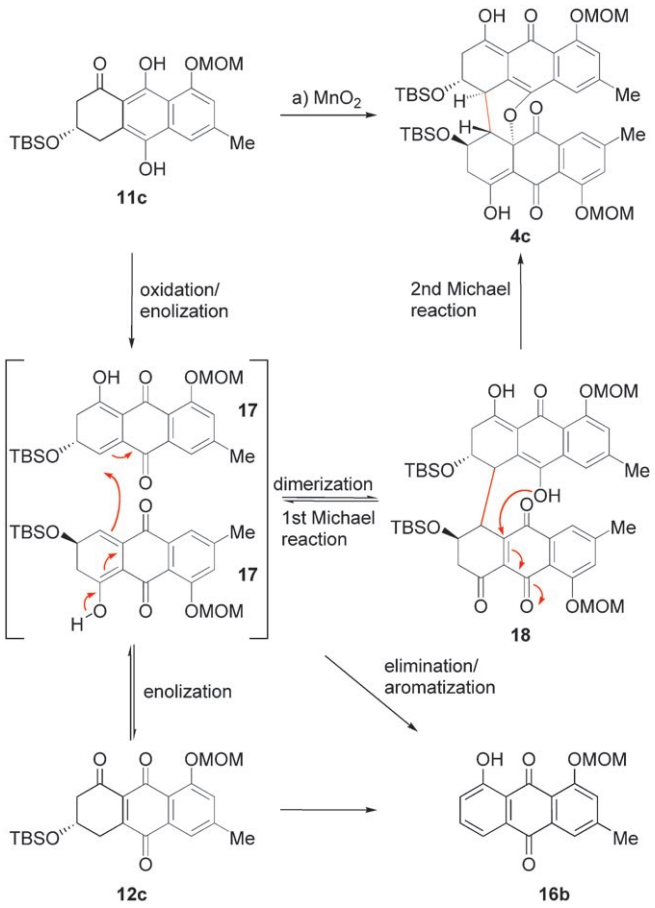

Scheme 3. Mechanistic investigation of the dimerization cascade (**11c** to **4c**). Reagents and conditions: a) MnO_2 (1.5 wt equiv), CH_2Cl_2 (0.35 M), 25 °C, 1 h, 20% **4c**; 30% **18**; 45% **16b**; 5% **12c**; ratio of products dependent on reaction time.

Keywords: anthraquinones · biomimetic synthesis · Michael reaction · natural products · total synthesis

Table 1: Selected physical properties for compounds **2a**, **2b**, **4c**, **12c**, **16b**, and **18**.

2a: $R_f = 0.53$ (benzene/acetone 2:1, oxalic acid impregnated TLC); ^{1}H NMR (500 MHz, [D$_8$]THF): $\delta = 14.60$ (2H, s), 12.10 (2H, s), 7.19 (2H, d, $J = 2.3$ Hz), 6.79 (2H, d, $J = 2.3$ Hz), 4.49 (2H, d, $J = 4.8$ Hz), 3.92 (6H, s), 3.41 (2H, br), 2.85 ppm (2H, d, $J = 4.8$ Hz); ^{13}C NMR (125 MHz, [D$_8$]THF): $\delta = 194.3$, 186.5, 182.5, 167.1, 165.5, 135.2, 111.8, 108.0, 107.4, 107.1, 69.9, 67.9, 59.0, 56.4, 49.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{21}O_{12}^-$ $[M-H]^-$: 573.1038; found: 573.1031.

2b: $R_f = 0.50$ (benzene/acetone 4:1, oxalic acid impregnated TLC); ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 14.70$ (2H, s), 11.39 (2H, s), 7.46 (2H, s), 7.20 (2H, s), 4.39 (2H, d, $J = 6.0$ Hz), 3.37 (2H, s), 2.78 (2H, d, $J = 6.0$ Hz), 2.43 ppm (6H, s); ^{13}C NMR (125 MHz, [D$_8$]THF): $\delta = 186.0$, 184.6, 162.8, 160.4, 148.7, 133.5, 124.7, 121.3, 115.7, 107.6, 70.1, 68.0, 59.3, 49.5, 22.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{21}O_{10}^-$ $[M-H]^-$: 541.1140; found: 541.1136.

4c: $R_f = 0.43$ (MeOH/CH_2Cl_2 2:100); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 16.28$ (1H, s), 14.79 (1H, s), 7.20 (1H, br), 6.81 (1H, br), 6.53 (1H, br), 6.30 (1H, br), 5.47–5.44 (2H, m), 5.36–5.30 (2H, m), 4.48 (1H, ddd, $J = 11.0$, 11.0, 4.8 Hz), 4.15 (1H, ddd, $J = 11.0$, 11.0, 4.8 Hz), 3.62 (3H, s), 3.57 (3H, s), 3.32 (1H, d, $J = 11.0$ Hz), 3.08 (1H, d, $J = 11.0$ Hz), 3.06 (1H, dd, $J = 17.8$, 4.8 Hz), 2.87 (1H, dd, $J = 17.8$, 4.8 Hz), 2.74 (1H, dd, $J = 17.8$, 11.0 Hz), 2.66 (1H, dd, $J = 17.8$, 11.0 Hz), 2.17 (3H, s), 1.99 (3H, s), 0.98 (9H, s), 0.94 (9H, s), 0.25 (3H, s), 0.20 (3H, s), 0.07 (3H, s), 0.00 ppm (3H, s).

12c: $R_f = 0.13$ (MeOH/CH_2Cl_2 1:100); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.10$ (1H, s), 7.00 (1H, s), 5.20 (2H, s), 4.55 (1H, br), 3.63–3.53 (2H, m), 3.52 (3H, s), 2.88–2.81 (1H, m), 2.83–2.79 (1H, m), 2.23 (3H, s), 0.79 (9H, s), 0.10 (3H, s), 0.07 ppm (3H, s).

16b: $R_f = 0.85$ (MeOH/CH_2Cl_2 5:100); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 13.03$ (1H, s), 7.85 (1H, brs, 7.78 (1H, d, $J = 7.5$ Hz), 7.62 (1H, dd, $J = 7.5$, 8.5 Hz), 7.29 (1H, d, $J = 8.5$ Hz), 7.39 (1H, brs), 5.41 (2H, s), 3.60 (3H, s), 2.51 (3H, s) ppm (3H, s); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{14}O_5Na^+$ $[M+Na]^+$: 321.0733; found: 321.0731.

18: $R_f = 0.24$ (MeOH/CH_2Cl_2 2:100); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 16.24$ (1H, s), 7.59 (1H, s), 7.49 (1H, s), 7.40 (1H, s), 7.34 (1H, s), 5.39–5.37 (2H, m), 5.33–5.31 (2H, m), 4.41–4.40 (1H, m), 4.31–4.29 (1H, m), 4.06–4.05 (1H, m), 3.90–3.89 (1H, m), 3.61 (3H, s), 3.56 (3H, s), 3.00 (1H, dd, $J = 5.3$, 1.8 Hz), 2.48 (3H, s), 2.46 (3H, s), 2.17–2.13 (2H, m), 2.00 (2H, dd, $J = 18.5$, 3.5 Hz), 0.74 (9H, s), 0.63 (9H, s), 0.13 (3H, s), 0.03 (3H, s), −0.08 (3H, s), −0.11 ppm (3H, s).

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[8] The enantiomeric ratio (e.r.) of compound **6a** was determined by Mosher ester analysis (^{1}H NMR and HPLC) to be 85:15. Optimization of this desymmetrization reaction is currently underway. The e.r. of **6b** was assumed to be the same (i.e. 98:2) as in reference [7].

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[10] The impurities that impeded the cascade were carried through from the Hauser annulation and were not batch specific.

[11] CCDC-286831 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] For a review highlighting a number of cascade reactions in total synthesis, see: K. C. Nicolaou, T. Montagnon, S. N. Snyder, *Chem. Commun.* **2003**, 551–564.

