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# Scope and Optimization of the Double Knorr Cyclization: Synthesis of Novel Symmetrical and Unsymmetrical Tricyclic 1,8-Diazaanthraquinones

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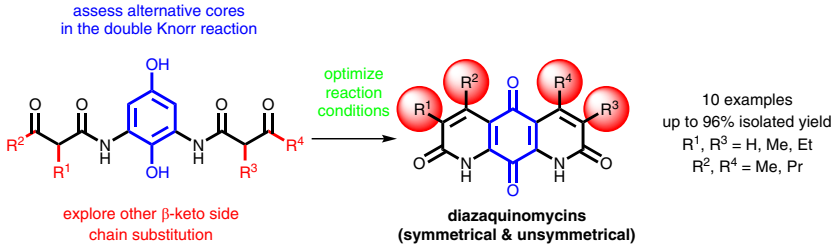


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**Abstract** The Knorr cyclization of β-ketoanilides to form 2-quinolones in the presence of acid is well documented chemistry. Double Knorr cyclization is rare, with very few examples appearing in the literature to date. The double Knorr methodology can provide access to tricyclic 1,8-diazaanthraquinones, a scaffold seen in the diazaquinomycin family. The optimized synthesis of diazaquinomycin A and structural analogues thereof via double Knorr cyclization of di-β-ketoanilide precursor substrates is reported. The scope and generality of the double Knorr cyclization were investigated along with an optimization study. The double Knorr cyclization was found to be sensitive to steric bulk on precursor substrates. In addition, the presence of a 5-hydroxy group on the 1,3-di-β-ketoanilide facilitated the double Knorr cyclization, possibly due to its stabilizing effect on the carbocation intermediates formed during the reaction.

**Key words** diazaquinomycin A, double Knorr methodology, cyclization, di-β-ketoanilide, 1,8-diazaanthraquinone

In 2015, the World Health Organization reported more than 10 million new cases of tuberculosis (TB) and approximately 1.8 million deaths worldwide, predominantly in developing countries.[1] Tuberculosis is a bacterial infection caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and is spread from person to person through the air.[1] The occurrence of cases of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) is of growing concern, highlighting the importance and clinical need for continued anti-TB drug discovery efforts.[2,3]

A recent report showed diazaquinomycins A, H, and J (Figure 1) to be potent and selective antibacterial agents against *M. tuberculosis* (MIC range 0.04–0.10 μg/mL) and exhibited no cell cytotoxicity against Vero cells (ATCC CRL-1586) at 28 μM, the highest concentration tested.[4] Strikingly, diazaquinomycin A retained excellent anti-TB activity against common drug-resistant strains of *M. tuberculosis* with MIC values in the range of 0.06–0.27 μg/mL.[4]

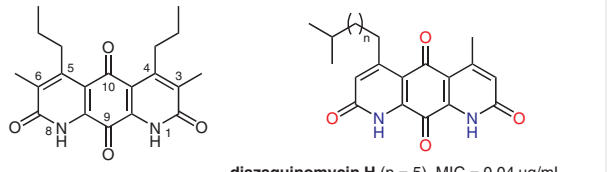
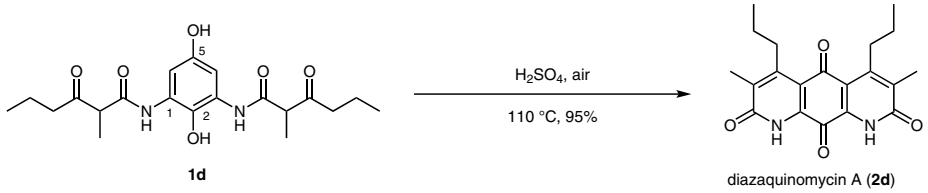



**Figure 1** Diazaquinomycins A, H, and J show excellent anti-TB activity

The remarkable anti-TB activities reported for diazaquinomycins A, H, and J along with low cytotoxicity profile prompted us to establish a robust and modular synthetic route that will be used to efficiently construct a compound library of symmetrical and unsymmetrical diazaquinomycin analogues. The synthetic route should allow for structural variations on the 3, 4, 5, and 6 positions of the diazaquinomycin scaffold, facilitating future structure-activity relationship (SAR) studies. Although synthetic routes to access analogous compounds are known,[5–9] we became particularly interested in exploring and expanding upon an uncommon route that utilizes a double Knorr cyclization as the key ring forming step, pioneered by Kelly et al.[5] Knorr cyclization to form 2-quinolones from β-ketoanilides in the presence of acid is well documented chemistry; however, double Knorr cyclization remains underexplored. To the best of our knowledge, only one example of a successful double Knorr cyclization has appeared in the literature to date and is shown in Scheme 1.[5]

In this example, the symmetrical di-β-ketoanilide **1d** having a 2,5-dihydroquinone core underwent double Knorr cyclization in hot sulfuric acid, open to air, providing diazaquinomycin A (**2d**) in excellent yield.[5] Notably, this ele-



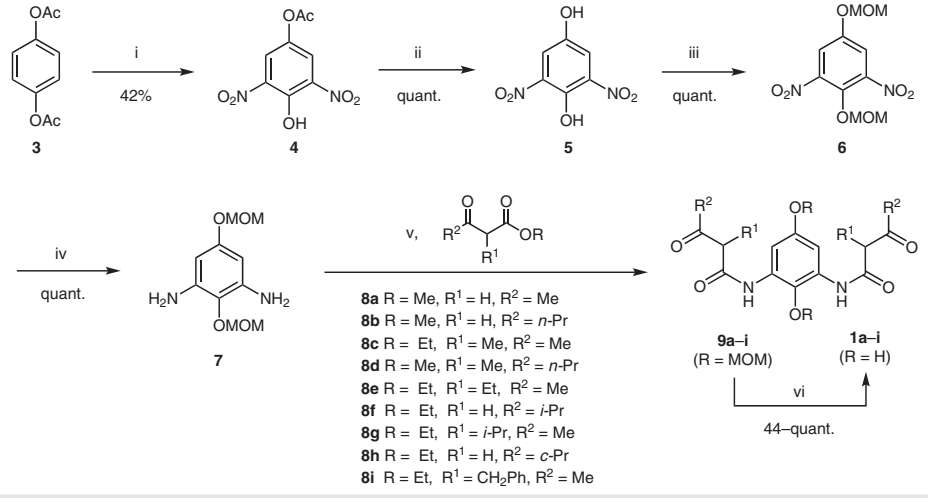

**Scheme 1** Double Knorr cyclization to form diazaquinomycin A[5]

gant chemistry has not yet been successfully expanded upon to access structural derivatives of diazaquinomycin A. Also as mentioned by Kelly et al., an attempted double Knorr cyclization of a variant of substrate **1d** was reported in 1973; however, this reaction failed despite trying various reaction conditions.[10]

More recently, preliminary studies in published Ph.D. theses suggested that the double Knorr methodology reported by Kelly et al. could not be extended to other substrates.[11,12] Despite these unsuccessful reports, we remained optimistic that double Knorr cyclization methodology can be used to access other diazaquinomycin derivatives.

In this work, we expand the double Knorr methodology to construct symmetrical and unsymmetrical analogues of diazaquinomycin A. We also probe the double Knorr reaction to gauge its tolerance to changes in steric bulk in the di-β-ketoanilide side chains, optimize the reaction conditions, and investigate what impact alternative cores (other than 2,5-hydroquinone) have on the double Knorr cyclization.

To start, a series of symmetrical di-β-ketoanilides **1a–i** having a 2,5-dihydroquinone core were synthesized according to Scheme 2 by following the Kelly route[5] with modifications. Commercially available 1,4-diacetoxybenzene (**3**) was nitrated using 70% nitric acid to provide the dinitro derivative **4** in 42% yield.[13] The acetyl group was removed by refluxing **4** in methanol and hydrochloric acid to give the phenol **5** in quantitative yield.[14] The phenolic groups of **5** were protected using chloromethylmethyl ether (MOM-Cl) and diisopropylethylamine (DIPEA) in tetrahydrofuran, affording pure di-O-MOM protected product **6** in quantitative yield.[5] Compound **6** was found to gradually decompose (loss of a MOM group) in methanol (as seen by HPLC monitoring) but was stable in ethyl acetate (see Table S1 in Supporting Information). The reduction of the nitro groups in **6** was therefore performed using palladium/carbon and hydrogen in ethyl acetate. This provided diamine **7** in quantitative yield after filtration of the reaction mixture through Celite and evaporation of the filtrate. The symmetrical di-β-ketoanilides **9a–i** were obtained in good to excellent yields by heating diamine **7** in excess β-keto ester **8a–i** followed by flash column chromatography.[5] A literature O-MOM deprotection procedure [1 M HCl/THF/acetone (1:1:1) at 65 °C][5] was employed to deprotect our series of di-β-ketoanilides **9a–i** and provide the corresponding di-β-ketoanilide hydroquinones **1a–i** in good to excellent yields.




**Scheme 2** Synthesis of symmetrical di-β-ketoanilides **1a–i**. *Reagents and conditions*: (i) 70% $HNO_3$, 20 °C, 2 h; (ii) HCl/MeOH, reflux, 2 h; (iii) MOM-Cl, DIPEA, THF, 25 °C, 18 h; (iv) 10% Pd/C, 1.4 bar $H_2$, EtOAc, 45 °C, 18 h; (v) neat, 130–200 °C, 1–5 h, 39–74% yield; (vi) 1 M HCl/THF/acetone (v/v/v, 1:1:1), 65 °C, 1 h.

The symmetrical di-MOM protected di-β-ketoanilides **9c–e**, **g**, and **i** were predicted to form as a mixture of stereoisomers since the corresponding β-keto esters used (**8c–e**, **g**, and **i**) were racemic. As expected, two enantiomers (*R*,*R* and *S*,*S*) and one *meso* compound (*R*,*S* = *S*,*R*) were formed in each case with a stereoisomeric ratio of 1:1:2, respectively. This was confirmed using $^1$H NMR spectroscopy and chiral HPLC. In all these cases, the diastereotopic methylene protons of the O-MOM protecting group appeared as two doublets for the enantiomeric pair and a singlet for the *meso* isomer in their $^1$H NMR spectra when $CDCl_3$ was used as a solvent. Interestingly, when the $^1$H NMR spectrum was recorded in DMSO-$d_6$, the signals associated with these methylene protons coalesced into one singlet.

As noted previously,[15] this observed signal coalescence in DMSO-$d_6$ is most likely caused by solvent dependent effect, in which DMSO-$d_6$ is involved in the interconversion process of these diastereotopic methylene protons. Taking **9d** (Figure 2, A) as an example, its $^1$H NMR spectra (recorded in $CDCl_3$ and DMSO-$d_6$) and chiral HPLC chromatogram are shown in Figure 2 (B and C), respectively. In $CDCl_3$ the diastereotopic methylene protons resonate as two doublets at 4.94 and 5.09 ppm (enantiomeric pair) as well as a singlet at 5.02 ppm (*meso* form), however, in DMSO-$d_6$ the same methylene protons appear as one singlet (4.91 ppm). A discrepancy was found when comparing our $^1$H NMR data for **9d** with published data for the same compound.[5] Specifically, the literature $^1$H NMR data for **9d** (recorded in $CDCl_3$) did not report the singlet that we observed at 5.02 ppm. To clarify this discrepancy, we contacted and consulted with Prof. T. Ross Kelly who suggested that one of the diastereomeric forms (*meso*) might have been lost during their column purification and/or recrystallization process (personal communication).

It is known that Knorr cyclization generally requires heating in the presence of strong acids.[16,17] The first and only report of a successful double Knorr cyclization was carried out at 110 °C in concentrated sulfuric acid.[5] The symmetrical di-β-ketoanilide 2,5-hydroquinone substrates **1a–i** were therefore subjected to these reported cyclization conditions (110 °C in sulfuric acid) to gauge their suitability as double Knorr substrates. In each case the reaction progress was monitored by HPLC and the results are shown in Table 1.

The double Knorr cyclization of unhindered substrates **1a–e** proceeded smoothly to give 1,8-diazaanthraquinones **2a–e** in good to excellent yields (Table 1, entries 1–5). Isolation of pure 1,8-diazaanthraquinones **2a–e** was achieved by precipitation in ice-water followed by centrifugation, removal of supernatant, and washing the solids with additional cold water until the pH of supernatant became neutral. This method proved easier than filtration procedure because in our hands the 1,8-diazaanthraquinones formed fine suspensions in water that easily passed through the filter paper during filtration. Overall, the sterically hindered di-β-ketoanilides **1f–i** were found to be poor substrates for the double Knorr cyclization (entries 6–9). When α-carbonyl substitution on the β-ketoanilide side chain is changed to bulkier isopropyl (*i*-Pr), cyclopropyl (*c*-Pr), or benzyl groups, the double Knorr cyclization pathway is not favorable. Instead, a complex mixture of products formed, with single Knorr cyclization and acid-mediated amide hydrolysis reaction pathways dominating, an observation that is consistent with literature reports.[5,10]

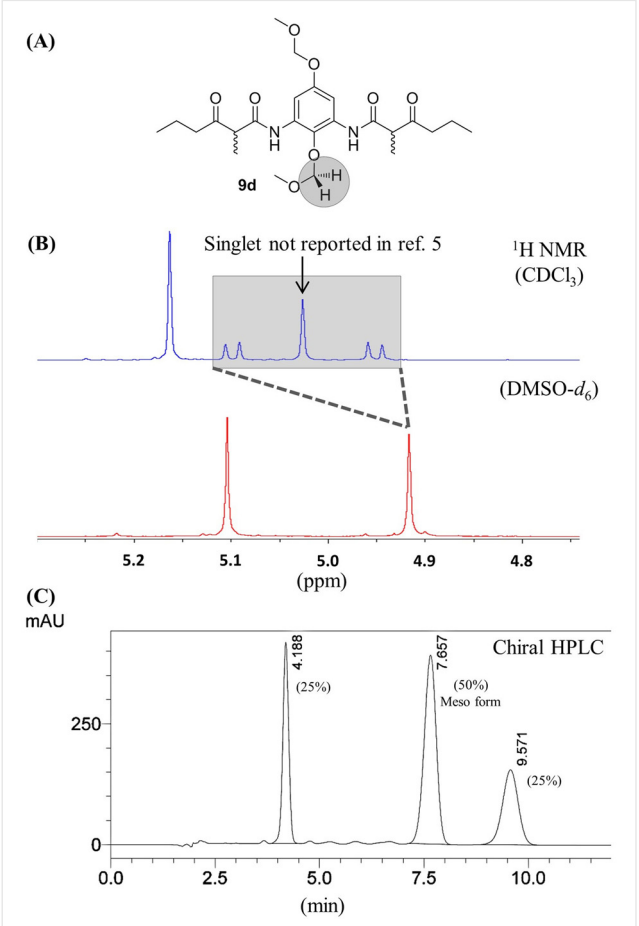
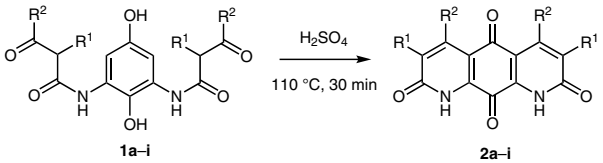



**Figure 2** A: Structure of **9d** highlighting diastereotopic methylene protons of interest; B: Magnified regions of $^1$H NMR spectra (recorded at 400 MHz) of **9d** in $CDCl_3$ and DMSO-$d_6$, respectively; C: Chiral HPLC chromatogram of **9d**, showing the *meso* form (50%) and two enantiomers (25% each). Chiral HPLC was performed using an analytical HPLC (Shimadzu LC-20A series) equipped with a Lux 5 µm Amylose-1 column (150 mm × 4.6 mm, Phenomenex) and flow rate of 1 mL/min. Mobile phase conditions: hexane/EtOH/TFA (65:35:0.1, v/v/v) (isocratic elution), UV detection at 254 nm and 220 nm.

Next, to further explore the scope of the double Knorr methodology and potentially improve the cyclization of sterically hindered di-β-ketoanilides, an optimization study was performed by varying the solvent/reagent and temperature. The results are shown in Table 2. At 110 °C, the

double Knorr cyclization was complete after 1 minute in sulfuric or triflic acid (Table 2, entries 1 and 5). Traces of unidentified by-products were formed at 110 °C resulting in an 88% and 82% yield of **2d**, respectively. It was found that lowering the temperature to 50 °C resulted in less by-product formation, allowing for higher yields for **2d** in both sulfuric acid (94%) and triflic acid (>99%) (entries 2 and 6). Interestingly, the double Knorr cyclization occurred smoothly even at ambient temperature (25 °C), giving quantitative conversions of **1d** into **2d** (entries 4 and 7). At room temperature, the double Knorr cyclization proceeded faster in triflic acid and was complete after 50 minutes compared to 4 hours in sulfuric acid (Table 2, entry 4 vs entry 7). Our observation that triflic acid was a superior solvent for Knorr cyclization is in agreement with literature findings.[16]

**Table 1** Symmetrical Double Knorr Cyclization of **1a–i** to **2a–i**

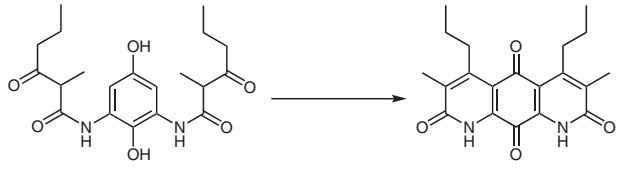



**1a–i** **2a–i**

| Entry | Product | $R^1$ | $R^2$ | Yield (%)[a] | Retention time (min) |
|---|---|---|---|---|---|
| 1 | **2a** | H | Me | 69 (67) | 5.32 |
| 2 | **2b** | H | *n*-Pr | 86 (70) | 6.23 |
| 3 | **2c** | Me | Me | 92 (75) | 5.78 |
| 4 | **2d** | Me | *n*-Pr | 88 (74) | 6.77 |
| 5 | **2e** | Et | Me | 81 (61) | 6.25 |
| 6 | **2f** | H | *i*-Pr | 13 | 6.17 |
| 7 | **2g** | *i*-Pr | Me | 7 | 6.86 |
| 8 | **2h** | H | *c*-Pr | 0 | – |
| 9 | **2i** | $CH_2Ph$ | Me | 0 | – |

[a] Yield observed by HPLC (254 nm), numbers in parentheses indicate isolated yield.

**Table 2** Survey of Double Knorr Cyclization Reaction Conditions (**1d** to **2d**)



**1d** **2d**

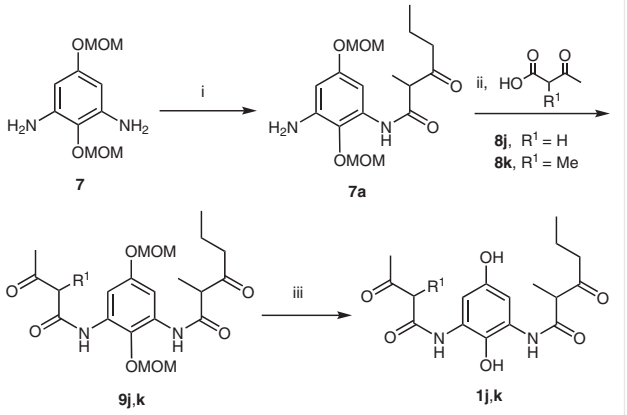
| Entry | Solvent/reagent | Temp (°C) | Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | $H_2SO_4$ | 110 | 1 | 88 |
| 2 | $H_2SO_4$ | 50 | 25 | 94 |
| 3 | $H_2SO_4$ | 25 | 50 | 73 |
| 4 | $H_2SO_4$ | 25 | 240 | >99 |
| 5 | TfOH | 110 | 1 | 82 |
| 6 | TfOH | 50 | 25 | >99 (95) |
| 7 | TfOH | 25 | 50 | >99 |
| 8 | $Ph_2O$ | 110 | 30 | NR[b] |
| 9 | $Ph_2O$ | 210 | 30 | 26 |

[a] Yield observed by HPLC (254 nm), number in parentheses indicates isolated yield.
[b] NR: No reaction.

A thermally induced double Knorr cyclization was also attempted using diphenyl ether as solvent. At 110 °C, no reaction took place with only starting material recovered, as seen by HPLC analysis on the reaction mixture (Table 2, entry 8). When the temperature was raised to 210 °C, the starting material was consumed within 30 minutes and the double Knorr product **2d** was formed in 26% yield along with a single Knorr cyclized, but side chain hydrolyzed, by-product (74%). Attempts were made to cyclize the sterically hindered substrate **1g** into **2g** using milder conditions such as triflic acid at 25 or 50 °C. In both cases, HPLC reaction monitoring showed that starting material **1g** was rapidly consumed; however, double cyclized product **2g** could not be obtained in the reaction mixture comprised of predominantly hydrolyzed and monocyclized by-products. Moreover, decreasing the reaction concentration by 50-fold in an effort to favor an intramolecular cyclization process did not improve the reaction outcome.

To expand the scope of the double Knorr substrates, we envisioned that this methodology can be extended to access unsymmetrical 1,8-diazaanthraquinones by simply employing unsymmetrical di-β-ketoanilide 2,5-hydroquinone substrates in the double Knorr reaction. To validate this, unsymmetrical substrates **1j**,**k** were synthesized according to Scheme 3. The mono-β-ketoanilide **7a** was obtained by coupling **7** with 2-methyl-3-oxohexanoic acid (0.7 equiv) using EDC in 25% yield after flash chromatography to remove remaining diamine **7** and traces of di-β-ketoanilide **9d**. The unsymmetrical di-β-ketoanilides **9j**,**k** were obtained using EDC coupling with corresponding β-keto acids **8j** or **8k** in 86% and 78% yield, respectively. Removal of MOM protecting groups using 1 M HCl/THF/acetone (1:1:1, v/v/v) at 65 °C furnished **1j**,**k** in moderate to good yields. As expected, the unsymmetrical di-β-ketoanilide hydroquinones **1j**,**k** were smoothly converted into 1,8-diazaanthraquinones **2j**,**k** in excellent yields using the optimized double Knorr cyclization conditions (Table 3, entries 1 and 2).

Lastly, we investigated what impact the central core structure had on the double Knorr cyclization. Specifically, we wanted to probe the importance of the 2- and 5-hydroxy groups. The monohydroxy di-β-ketoanilides **10** and **11** were synthesized (Schemes S1 and S2; Supporting

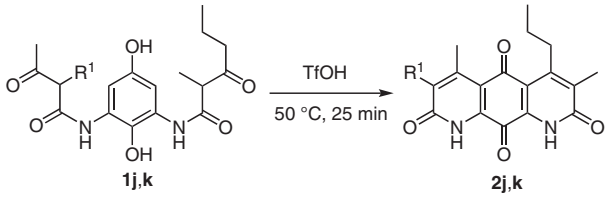



**Scheme 3** Synthesis of unsymmetrical di-β-ketoanilides **1j,k**. *Reagents and conditions*: (i) 2-methyl-3-oxohexanoic acid, EDC·HCl, DMAP, $CH_2Cl_2$, r.t., 30 min, 25%; (ii) **8j** or **8k**, EDC·HCl, DMAP, $CH_2Cl_2$, r.t., 30 min, **9j** (86%) or **9k** (78%); (iii) 1 M HCl/THF/acetone (1:1:1, v/v/v), 65 °C, 1 h; **1j** (78%) or **1k** (57%).

Information) and tested as double Knorr cyclization substrates (Scheme 4).

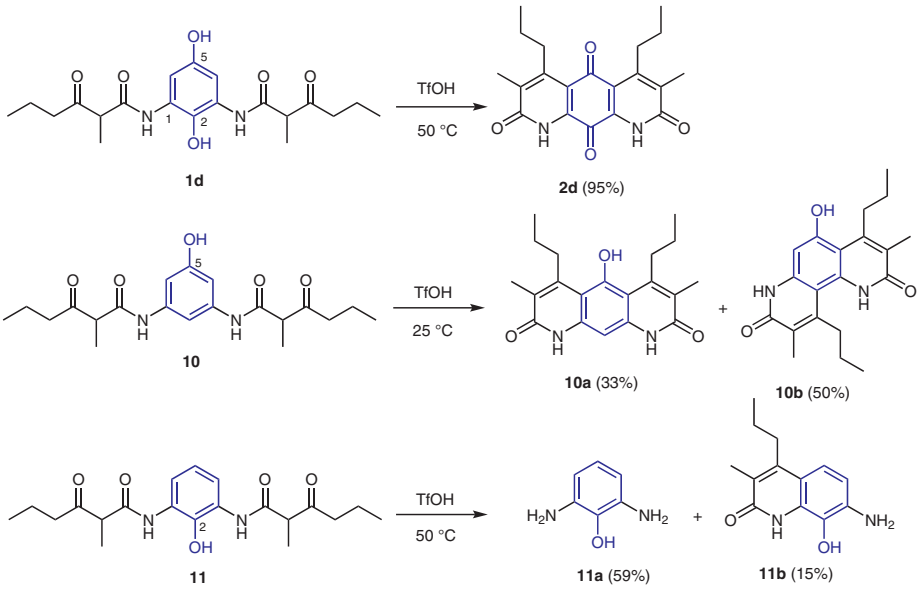
Interestingly, **10** having a 5-hydroxy group successfully cyclized to form two inseparable regioisomeric tricyclic double Knorr products in triflic acid (25 °C) in 83% combined yield. The linear isomer **10a** and angular isomer **10b** were formed in 2:3 ratio, respectively, and their structures were validated using $^1$H NMR and HRMS (see Supporting Information). In sulfuric acid (110 °C), **10a** and **10b** were formed in a 91% combined yield but in a 1:4 ratio, respectively, based on $^1$H NMR analysis. Surprisingly, **11** having a 2-hydroxy group (Scheme 4) did not undergo double Knorr cyclization. Although starting material **11** was consumed during the reaction, a complex final reaction mixture resulted, which contained mostly hydrolyzed by-product **11a** (59%) along with monocyclized and hydrolyzed by-product **11b** (15%). These results were intriguing and highlighted the importance of the 5-hydroxy group on the 1,3-di-β-ketoanilide substrates in the double Knorr reaction. We believe that the *meta* positioning of the 5-hydroxy moiety relative to the 1,3-anilide groups in **1d** and **10** contributes to the stabilization (via resonance) of carbocation intermediates formed during this transformation, allowing the double Knorr cyclization to take place. A simplified mechanism that starts from two possible proposed monocyclized intermediates **17** and **18** is illustrated in Scheme 5. If the reaction proceeds from **17**, the lack of substitutions on both C-6 and C-8 positions accounts for the formation of linear regioisomer **10a** (path in green) and angular isomer **10b** (path

**Table 3** Unsymmetrical Double Knorr Cyclization of **1j,k** to **2j,k**




| Entry | Product | $R^1$ | Yield (%)[a] | Retention time (min) |
|---|---|---|---|---|
| 1 | **2j** | H | 96 | 6.06 |
| 2 | **2k** | Me | 94 | 6.28 |

[a] Isolated yield.

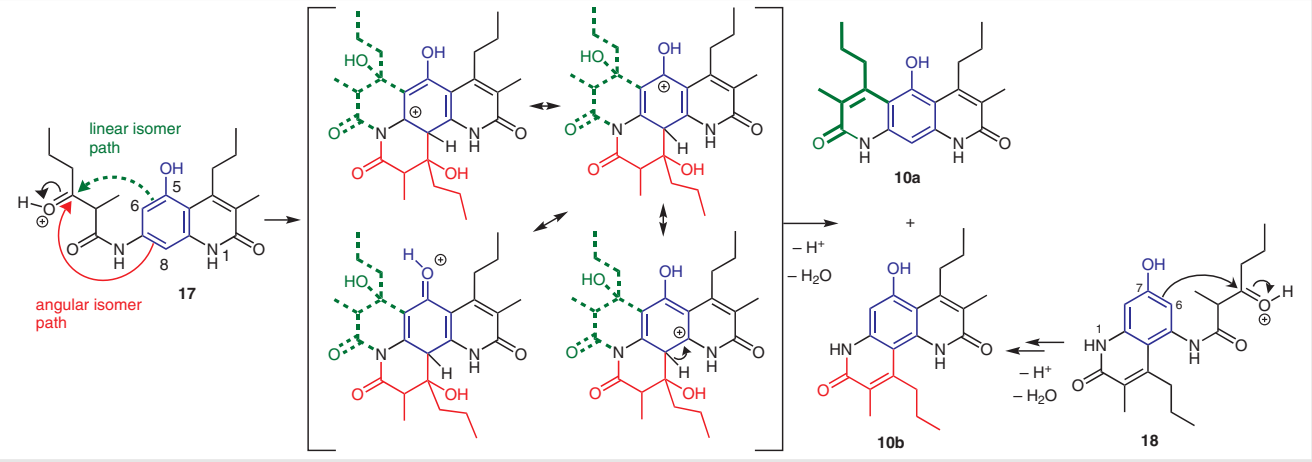



**Scheme 4** Assessment of di-β-ketoanilides **10** and **11** in the double Knorr reaction

in red, Scheme 5), respectively. However, if the reaction proceeds from **18**, only the angular isomer **10b** can be formed. Our proposed mechanisms also offer a potential explanation why **10b** was the major product and **10a** was minor under our examined reaction conditions.

Additional di-β-ketoanilides **12**–**16** (Figure 3) were also synthesized according to Schemes S3–S7 (see Supporting Information) and similarly screened as double Knorr cyclization substrates. Unfortunately, none of these di-β-ketoanilides underwent double Knorr cyclization despite trying a variety of reaction conditions. Instead, complex mixtures containing predominantly hydrolysis and single Knorr-cyclized products were formed (vide supra). It should be noted, in the case of **16**, our finding also supported previous experimental data by Kelly et al., demonstrating the double Knorr cyclization occurred first, followed by oxidation from tricyclic 9,10-dihydroquinone to 9,10-quinone.[5]

In summary, we have demonstrated that the double Knorr cyclization of di-β-ketoanilide hydroquinones was an efficient synthetic route to access symmetrical and unsymmetrical tricyclic 1,8-diazaanthraquinone analogues of the diazaquinomycin family. The scope and generality of the double Knorr cyclization was investigated along with an optimization study and it was found that the double Knorr cyclization is sensitive to increased steric bulk on precursor substrates. The unhindered di-β-ketoanilides **1a**–**e** successfully cyclized to give 1,8-diazaanthraquinones **2a**–**e** in excellent yields. In addition, the unsymmetrical di-β-ketoanilides **1j**,**k** similarly cyclized to provide unsymmetrical 1,8-diazaanthraquinones **2j**,**k** in excellent isolated yields. An optimization study using **1d** as a model substrate showed that the double Knorr cyclization can occur smoothly in triflic acid at 50 °C to give **2d** in excellent isolated yield (95%) after 25 minutes. Moreover, the double Knorr reaction proceeded faster in triflic acid compared to sulfuric acid. An assessment of alternative cores validated the importance of the 5-hydroxy group that resides *meta* to the 1,3-β-ketoanilide groups. The di-β-ketoanilides **1d** and **10** both have a 5-hydroxy moiety and were the only cores in our substrate library to undergo double Knorr cyclization in sulfuric or triflic acid. It is also hypothesized that the 5-hydroxy group of 1,3-β-ketoanilides plays a stabilizing role in carbocation intermediates, enabling double Knorr cyclization reaction. Synthesis and antituberculosis evaluation of unsymmetrical diazaquinomycins H and J as well as an expanded series of diazaquinomycin derivatives are ongoing, and will be reported in due course.




**Scheme 5** Proposed mechanism and resonance structures of carbocation intermediates accounting for the stabilizing role of the 5-hydroxy group of 1,3-di-β-ketoanilide in double Knorr cyclization

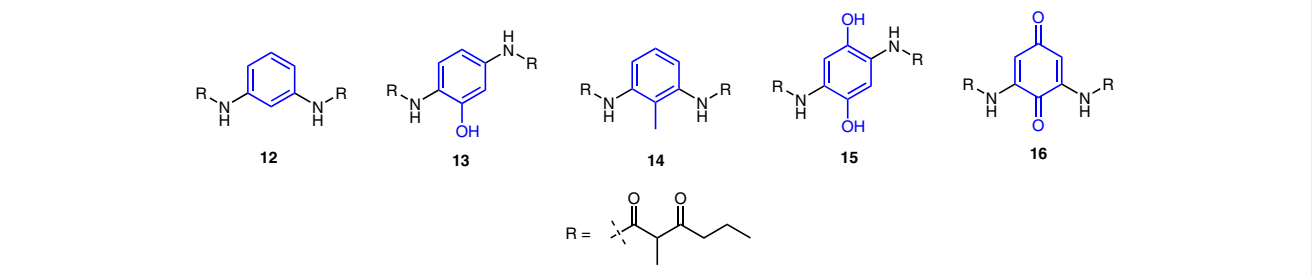



**Figure 3** Di-β-ketoanilide cores failed to undergo double Knorr cyclization

Solvents and reagents were purchased from Sigma-Aldrich, Acros, or Fisher Scientific, and used without further purification. Reactions were monitored either by TLC or by analytical HPLC employing a Shimadzu LC-20A series high-performance liquid chromatography (HPLC) system. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III HD-400 (ultrashield) spectrometer (400 MHz and 100 MHz, respectively). All chemical shifts are given as δ value (ppm) and coupling constants, *J*, are reported in hertz (Hz). NMR solvent peaks were referenced as follows: ($^1$H NMR) $CDCl_3$: 7.27 ppm, DMSO-$d_6$: 2.50 ppm; ($^{13}$C NMR) $CDCl_3$: 77.23 ppm, DMSO-$d_6$: 39.51 ppm. High-resolution mass spectroscopy data was obtained using an Agilent 6530 Q-TOF LC/MS. Low-resolution mass spectroscopy data was obtained using an Agilent 6120 single quad MS using direct injection. $H_2$ for hydrogenation reactions was generated on site using a domnick hunter NITROX UHP-60H hydrogen generator, USA. Melting points were determined in open capillary tube using a Büchi B-540 melting point apparatus. Compounds were purified by flash chromatography on silica gel using a Biotage Isolera One system. The purity of compounds was determined by analytical HPLC (Shimadzu LC-20A series) using a Gemini, 3 µm, C18, 110 Å column (50 mm × 4.6 mm, Phenomenex) and flow rate of 1 mL/min. Gradient conditions: solvent A (0.1% TFA in $H_2O$) and solvent B (MeCN): 0–2.0 min 100% A, 2.0–7.0 min 0–100% B (linear gradient), 7.0–8.0 min 100% B, UV detection at 254 nm and 220 nm.

**Removal of MOM Protecting Groups; *N,N′*-(2,5-Dihydroxy-1,3-phenylene)bis(3-oxobutanamide) (1a); Typical Procedure**

Compound **9a** (115 mg, 0.29 mmol) was dissolved in 1 M HCl/THF/acetone (1:1:1, 40 mL) and stirred at 65 °C for 1 h. Once the reaction was complete (seen by TLC analysis), the reaction was diluted with EtOAc (200 mL) and washed with $H_2O$ (2 × 100 mL). The organic layer was dried (anhyd $Na_2SO_4$), filtered, and concentrated to give **1a** (89 mg, 0.29 mmol, quant.) as a light brown solid that was used directly without further purification; mp 174–176 °C; $R_f$ = 0.31 (hexane/EtOAc, 1:4).

HPLC purity: 92.4% (254 nm), 95.7% (220 nm); $t_R$ = 4.99 min.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.77 (s, 2 H), 9.01 (s, 1 H), 8.73 (s, 1 H), 6.99 (s, 2 H), 3.67 (s, 4 H), 2.19 (s, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 203.1, 166.0, 149.9, 131.1, 127.9, 104.8, 51.5, 30.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_6^+$: 309.1081; found: 309.1074; *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}N_2O_6Na^+$: 331.0901; found: 331.0890.

***N,N′*-(2,5-Dihydroxy-1,3-phenylene)bis(3-oxohexanamide) (1b)**

Yield: 45 mg (82%) (0.12 mmol scale); viscous light brown oil after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); $R_f$ = 0.19 (hexane/EtOAc, 1:1).

HPLC purity: 97.2% (254 nm), 97.2% (220 nm); $t_R$ = 6.08 min.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.78 (s, 2 H), 9.01 (br s, 1 H), 8.74 (s, 1 H), 6.98 (s, 2 H), 3.65 (s, 4 H), 2.52 (t, *J* = 7.18 Hz, 4 H), 1.45–1.56 (m, 4 H), 0.86 (t, *J* = 7.34 Hz, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 205.0, 166.0, 149.9, 131.1, 127.9, 104.7, 50.8, 44.1, 16.4, 13.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_6^+$: 365.1707; found: 365.1710; *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}N_2O_6Na^+$: 387.1527; found: 387.1529.

***N,N′*-(2,5-Dihydroxy-1,3-phenylene)bis(2-methyl-3-oxobutanamide) (1c)**

Yield: 36 mg (61%) (0.18 mmol scale); sticky light brown solid as a mixture of enantiomers (*R,R* and *S,S*) and *meso* form (*S,R* = *R,S*) after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); mp 122–124 °C (dec.); $R_f$ = 0.11 (hexane/EtOAc, 1:1).

HPLC purity: 99.5% (254 nm), 98.9% (220 nm); $t_R$ = 5.48 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.12 (br s, 2 H), 8.70 (br s, 1 H), 7.08 (s, 2 H), 3.64 (q, *J* = 7.21 Hz, 2 H), 2.29 (s, 6 H), 1.48 (d, *J* = 7.21 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 207.3, 170.0, 150.2, 132.2, 127.4, 105.6, 54.9, 29.0, 15.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_6^+$: 337.1394; found: 337.1398; *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{20}N_2O_6Na^+$: 359.1214; found: 359.1214.

***N,N′*-(2,5-Dihydroxy-1,3-phenylene)bis(2-methyl-3-oxohexanamide) (1d)**

Yield: 209 mg (85%) (0.53 mmol scale); viscous light brown oil as a mixture of enantiomers (*R,R* and *S,S*) and *meso* form (*S,R* = *R,S*) after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); $R_f$ = 0.24 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.44 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 2 H), 9.20 (s, 2 H), 8.78 (br s, 2 H), 7.19 (s, 4 H), 3.64 (q, *J* = 7.31 Hz, 4 H), 2.60 (t, *J* = 7.14 Hz, 8 H), 1.58–1.70 (m, 8 H), 1.52 (d, *J* = 7.09 Hz, 12 H), 0.92 (t, *J* = 7.35 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.98, 209.96, 169.9, 150.5, 131.9, 127.5, 105.2, 54.2, 44.0, 17.0, 16.20, 16.16, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_6^+$: 393.2020; found: 393.2014; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_6Na^+$: 415.1840; found: 415.1835.

***N,N′*-(2,5-Dihydroxy-1,3-phenylene)bis(2-ethyl-3-oxobutanamide) (1e)**

Yield: 70 mg (62%) (0.19 mmol scale); viscous light brown oil as a mixture of enantiomers (*R,R* and *S,S*) and *meso* form (*S,R* = *R,S*) after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); $R_f$ = 0.19 (hexane/EtOAc, 1:1).

HPLC purity: 99.6% (254 nm), 98.0% (220 nm); $t_R$ = 5.93 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.25 (s, 2 H), 8.72 (br s, 1 H), 8.28 (br s, 1 H), 7.21 (s, 2 H), 3.55 (t, *J* = 7.09 Hz, 2 H), 2.33 (s, 6 H), 1.91–2.12 (m, 4 H), 1.00 (t, *J* = 7.58 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 207.60, 207.58, 168.9, 150.6, 131.9, 127.5, 105.3, 62.2, 30.2, 25.0, 24.9, 11.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_6^+$: 365.1707; found: 365.1711; *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}N_2O_6Na^+$: 387.1527; found: 387.1529.

***N,N′*-(2,5-Dihydroxy-1,3-phenylene)bis(4-methyl-3-oxopentanamide) (1f)**

Yield: 16 mg (44%) (0.044 mmol scale); white solid after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); mp 159–160 °C; $R_f$ = 0.24 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.02 min.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.79 (br s, 2 H), 9.02 (s, 1 H), 8.77 (s, 1 H), 6.98 (s, 2 H), 3.75 (s, 4 H), 2.67–2.81 (m, 2 H), 1.05 (d, *J* = 7.02 Hz, 12 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 208.6, 166.2, 149.9, 131.0, 127.9, 104.7, 48.8, 40.3, 17.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_6^+$: 365.1707; found: 365.1712; *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}N_2O_6Na^+$: 387.1527; found: 387.1531.

### *N*,*N*′-(2,5-Dihydroxy-1,3-phenylene)bis(2-acetyl-3-methylbutanamide) (1g)

Yield: 50 mg (87%) (0.13 mmol scale); sticky off-white solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*) after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); mp 62–64 °C; $R_f$ = 0.22 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.35 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 2 H), 9.14 (s, 2 H), 8.65 (s, 1 H), 8.63 (s, 1 H), 8.46 (br s, 2 H), 7.24 (s, 4 H), 3.39 (d, *J* = 9.29 Hz, 4 H), 2.35–2.44 (m, 4 H), 2.35 (s, 12 H), 1.05 (d, *J* = 7.03 Hz, 12 H), 1.03 (d, *J* = 7.03 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 208.33, 208.31, 168.1, 150.73, 150.71, 131.9, 127.6, 127.5, 105.1, 68.8, 32.6, 31.88, 31.86, 21.1, 20.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_6^+$: 393.2020; found: 393.2018; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_6Na^+$: 415.1840; found: 415.1837.

### *N*,*N*′-(2,5-Dihydroxy-1,3-phenylene)bis(3-cyclopropyl-3-oxopropanamide) (1h)

Yield: 104 mg (quant.) (0.29 mmol scale); light red-brown solid was used directly without further purification; mp 126–128 °C (dec.); $R_f$ = 0.23 (hexane/EtOAc, 1:1).

HPLC purity: 98.4% (254 nm), 98.7% (220 nm); $t_R$ = 5.67 min.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.84 (s, 2 H), 9.02 (br s, 1 H), 8.76 (s, 1 H), 6.99 (s, 2 H), 3.79 (s, 4 H), 2.08–2.17 (m, 2 H), 0.88–0.97 (m, 8 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 204.8, 165.8, 149.9, 131.0, 127.9, 104.7, 51.0, 20.6, 10.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}N_2O_6^+$: 361.1394; found: 361.1393; *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}N_2O_6Na^+$: 383.1214; found: 383.1217.

### *N*,*N*′-(2,5-Dihydroxy-1,3-phenylene)bis(2-benzyl-3-oxobutanamide) (1i)

Yield: 50 mg (73%) (0.10 mmol scale); viscous light brown oil as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*) after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); $R_f$ = 0.34 (hexane/EtOAc, 1:1).

HPLC purity: 99.3% (254 nm), 98.6% (220 nm); $t_R$ = 6.73 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 2 H), 8.99 (s, 2 H), 8.58 (br s, 2 H), 7.16–7.30 (m, 20 H), 7.04 (s, 4 H), 3.88 (t, *J* = 7.46 Hz, 4 H), 3.19–3.32 (m, 8 H), 2.16 (s, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.5, 168.3, 150.3, 137.2, 132.1, 129.0, 128.9, 127.3, 105.5, 62.9, 37.1, 30.61, 30.60.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{29}N_2O_6^+$: 489.2020; found: 489.2028; *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{28}N_2O_6Na^+$: 511.1840; found: 511.1854.

### *N*-[2,5-Dihydroxy-3-(3-oxobutanamido)phenyl]2-methyl-3-oxohexanamide (1j)

Yield: 50 mg (78%) (0.18 mmol scale); viscous light brown oil as a pair of enantiomers after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); $R_f$ = 0.13 (hexane/EtOAc, 1:1).

HPLC purity: 97.2% (254 nm), 97.2% (220 nm); $t_R$ = 5.79 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 9.17 (s, 1 H), 7.12 (d, *J* = 2.93 Hz, 1 H), 7.05 (d, *J* = 2.93 Hz, 1 H), 3.63 (s, 2 H), 3.63 (q, *J* = 7.27 Hz, 1 H), 2.59 (t, *J* = 7.25 Hz, 2 H), 2.28 (s, 3 H), 1.55–1.66 (m, 2 H), 1.48 (d, *J* = 7.09 Hz, 3 H), 0.90 (t, *J* = 7.46 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.7, 204.6, 170.0, 165.8, 150.2, 132.1, 127.6, 127.3, 105.5, 54.4, 49.5, 43.8, 31.1, 17.0, 15.6, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_6^+$: 351.1551; found: 351.1545; *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{22}N_2O_6Na^+$: 373.1370; found: 373.1364.

### *N*-[2,5-Dihydroxy-3-(2-methyl-3-oxobutanamido)phenyl]-2-methyl-3-oxohexanamide (1k)

Yield: 31 mg (57%) (0.15 mmol scale); viscous light brown oil as a mixture of two pairs of enantiomers (*R*,*R*; *S*,*S* and *S*,*R*; *R*,*S*) after flash column chromatography (hexane/EtOAc 9:1 to 1:1, v/v); $R_f$ = 0.19 (hexane/EtOAc, 1:1).

HPLC purity: 97.7% (254 nm), 97.1% (220 nm); $t_R$ = 6.01 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 9.12 (s, 1 H), 8.76 (br s, 1 H), 7.14 (s, 2 H), 3.64 (q, *J* = 7.09 Hz, 2 H), 2.60 (t, *J* = 7.09 Hz, 2 H), 2.32 (s, 3 H), 1.57–1.69 (m, 2 H), 1.52 (d, *J* = 7.18 Hz, 3 H), 1.51 (d, *J* = 7.18 Hz, 3 H), 0.91 (t, *J* = 7.46 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.9, 207.3, 170.0, 169.8, 150.4, 132.0, 127.5, 105.4, 105.3, 54.9, 54.2, 43.9, 29.1, 17.0, 16.01, 15.99, 15.42, 15.39, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_6^+$: 365.1707; found: 365.1712; *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}N_2O_6Na^+$: 387.1527; found: 387.1528.

### Symmetrical Double Knorr Cyclization; 4,5-Dimethyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (2a); Typical Procedure

$H_2SO_4$ (2 mL) was added to a 5 mL round-bottom flask containing **1a** (45 mg, 0.15 mmol), which was then placed in a preheated oil bath at 110 °C. The solution was stirred at 110 °C for 5 min open to air. The reaction was confirmed complete using HPLC analysis. The reaction mixture was poured onto ice and diluted to 20 mL using cold $H_2O$. The solid precipitate was collected by centrifugation. The supernatant was carefully decanted and the solid was washed with cold $H_2O$ (2 × 10 mL) using the centrifugation method. The solid was dried under vacuum to afford **2a** (26 mg, 0.10 mmol, 67%) as a brown solid; mp >300 °C (dec.); $R_f$ = 0.52 ($CH_2Cl_2$/MeOH, 9:1).

HPLC purity: 98.8% (254 nm), 95.6% (220 nm); $t_R$ = 5.32 min.

$^1$H NMR (400 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 7.13 (s, 2 H), 2.83 (s, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 179.9, 172.6, 163.7, 158.1, 136.6, 127.8, 119.2, 23.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_2O_4^+$: 271.0713; found: 271.0708.

### 4,5-Dipropyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (2b)

Yield: 15 mg (70%) (0.066 mmol scale); orange solid; mp 290 °C (dec.); $R_f$ = 0.50 ($CH_2Cl_2$/MeOH, 9:1).

HPLC purity: 98.8% (254 nm), 97.3% (220 nm); $t_R$ = 6.23 min.

$^1$H NMR (400 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 7.11 (s, 2 H), 3.13–3.22 (m, 4 H), 1.62–1.75 (m, 4 H), 1.11 (t, *J* = 7.34 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 179.9, 172.8, 163.8, 161.4, 136.8, 127.3, 118.6, 37.0, 23.2, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_4^+$: 327.1339; found: 327.1340.

### 3,4,5,6-Tetramethyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (2c)

Yield: 20 mg (75%) (0.089 mmol scale); red solid; mp >300 °C (dec.); $R_f$ = 0.47 ($CH_2Cl_2$/MeOH, 9:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm): $t_R$ = 5.78 min.

$^1$H NMR (400 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 2.75 (s, 6 H), 2.36 (s, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 181.7, 172.5, 163.0, 152.0, 151.9, 137.5, 133.7, 120.14, 120.11, 18.6, 13.43, 13.40.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_4^+$: 299.1026; found: 299.1031.

### 3,6-Dimethyl-4,5-dipropyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (2d)

Yield: 17 mg (95%) (0.051 mmol scale); red solid; mp 295 °C (dec); $R_f$ = 0.48 ($CH_2Cl_2$/MeOH, 9:1).

HPLC purity: 100.0% (254 nm), 97.6% (220 nm); $t_R$ = 6.77 min.

$^1$H NMR (400 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 3.06–3.14 (m, 4 H), 2.33 (s, 6 H), 1.54–1.66 (m, 4 H), 1.14 (t, *J* = 7.21 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 181.7, 172.8, 163.1, 154.2, 137.4, 134.0, 118.8, 32.7, 22.8, 14.7, 13.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_4^+$: 355.1652; found: 355.1666.

The spectroscopic data of **2d** are consistent with those of natural diazaquinomycin A.[18,19]

### 3,6-Diethyl-4,5-dimethyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (2e)

Yield: 26 mg (61%) (0.13 mmol scale); red solid; mp >300 °C (dec.); $R_f$ = 0.50 ($CH_2Cl_2$/MeOH, 9:1).

HPLC purity: 97.3% (254 nm), 98.4% (220 nm); $t_R$ = 6.25 min.

$^1$H NMR (400 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 2.84 (q, *J* = 7.58 Hz, 4 H), 2.74 (s, 6 H), 1.17 (t, *J* = 7.58 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 182.0, 172.6, 162.7, 150.2, 143.0, 133.7, 119.6, 20.8, 18.0, 12.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_4^+$: 327.1339; found: 327.1339.

### Unsymmetrical Double Knorr Cyclization; 3,5-Dimethyl-4-propyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (2j); Typical Optimized Procedure

Triflic acid (2 mL) was added to a 5 mL round-bottom flask containing **1j** (30 mg, 0.086 mmol), which was then placed in a preheated oil bath at 50 °C. The solution was stirred at 50 °C for 25 min open to air. The reaction was confirmed complete using HPLC analysis. The reaction mixture was poured onto ice and diluted to 15 mL using ice cold $H_2O$. The solid precipitate was collected by centrifugation. The supernatant was carefully decanted and the solid was washed with ice cold $H_2O$ (2 × 10 mL) using the centrifugation method. The solid was dried under vacuum to afford **2j** (26 mg, 0.083 mmol, 96%) as a red solid; mp >300 °C (dec); $R_f$ = 0.53 ($CH_2Cl_2$/MeOH, 9:1).

HPLC purity: 98.7% (254 nm), 97.3% (220 nm); $t_R$ = 6.06 min.

$^1$H NMR (400 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 7.10 (s, 1 H), 3.13–3.22 (m, 2 H), 2.82 (s, 3 H), 2.38 (s, 3 H), 1.55–1.70 (m, 2 H), 1.17 (t, *J* = 7.34 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 180.6, 172.8, 163.9, 163.5, 157.7, 156.0, 138.0, 136.3, 134.4, 127.8, 119.3, 118.9, 32.9, 23.1, 22.7, 14.5, 13.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_4^+$: 313.1183; found: 313.1176.

### 3,5,6-Trimethyl-4-propyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (2k)

Prepared from **1k** following the procedure for **2j**; yield: 23.5 mg (94%) (0.077 mmol scale); red solid; mp >300 °C (dec); $R_f$ = 0.51 ($CH_2Cl_2$/MeOH, 9:1).

HPLC purity: 99.5% (254 nm), 100.0% (220 nm); $t_R$ = 6.28 min.

$^1$H NMR (400 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 3.08–3.16 (m, 2 H), 2.73 (s, 3 H), 2.35 (s, 6 H), 1.56–1.68 (m, 2 H), 1.15 (t, *J* = 7.34 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/2% $CF_3CO_2D$): δ = 181.6, 172.7, 155.3, 151.1, 137.6, 137.4, 134.0, 133.5, 119.9, 119.1, 32.8, 22.8, 18.7, 14.6, 13.5, 13.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_4^+$: 327.1339; found: 327.1334.

### 4-Hydroxy-3,5-dinitrophenyl Acetate (4)[13]

The current procedure was adapted from Nissen et al.[13] with modification. 1,4-Diacetoxybenzene (**2**; 5.0 g, 25.7 mmol) was added portionwise to 70% $HNO_3$ at 0 °C. The reaction vessel was capped and allowed to warm to 20 °C followed by stirring at 20 °C for 2 h. The solution was poured onto ice and filtered. The solid was washed with cold $H_2O$ (100 mL) and air dried to afford **4** (2.61 g, 10.8 mmol, 42%) as a yellow solid; mp 94 °C (Lit.[13] mp 94 °C); $R_f$ = 0.18 (hexane/EtOAc, 1:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 11.35 (s, 1 H), 8.16 (s, 2 H), 2.37 (s, 3 H).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_7N_2O_7^+$: 243.0; found: 243.0; *m*/*z* [M + Na]$^+$ calcd for $C_8H_6N_2O_7Na^+$: 265.0; found: 265.0.

### 2,6-Dinitrobenzene-1,4-diol (5)[14]

The current procedure was adapted from Burger et al.[14] with modification. Concd HCl (1.0 mL) was added to a solution of **4** (2.0 g, 8.3 mmol) in MeOH (200 mL) and the solution was refluxed at 65 °C for 2 h. The solvent was removed using a rotary evaporator to give a solid that was recrystallized from toluene to afford **5** (1.65 g, 8.3 mmol, quant.) as an orange solid; mp 132–134 °C (Lit.[14] mp 132–136 °C); $R_f$ = 0.80 (EtOAc, 100%).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.85 (br s, 1 H), 10.51 (br s, 1 H), 7.61 (s, 2 H).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_5N_2O_6^+$: 201.0; found: 201.0; [M + Na]$^+$ calcd for $C_6H_4N_2O_6Na^+$: 223.0; found: 223.0.

### 2,5-Bis(methoxymethoxy)-1,3-dinitrobenzene (6)[5]

The current procedure was adapted from Kelly et al.[5] with modification. To a solution **5** (1.18 g, 5.9 mmol) in anhyd THF at 0 °C was added DIPEA (3.1 mL, 18.1 mmol) followed by MOM-Cl (1.7 mL, 22.1 mmol). The solution was allowed to warm to r.t. and stirred for 3 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with deionized $H_2O$ (2 × 200 mL). The organic layer was dried (anhyd

$Na_2SO_4$), filtered, and concentrated to give **6** (1.7 g, 5.9 mmol, quant.) as a yellow oil that was used directly without further purification; $R_f$ = 0.86 (hexane/EtOAc, 1:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 2 H), 5.24 (s, 2 H), 5.14 (s, 2 H), 3.50 (s, 3 H), 3.49 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 153.0, 146.6, 138.4, 116.6, 103.1, 95.3, 58.4, 56.8.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{12}N_2O_8Na^+$: 311.0; found: 311.0.

### 2,5-Bis(methoxymethoxy)benzene-1,3-diamine (7)

To a suspension of 10% Pd/C (120 mg) in EtOAc (35 mL) was added **6** (600 mg, 2.10 mmol). The reaction vessel was purged with $H_2$ (g) and the contents were stirred at 45 °C for 18 h at 1.4 bar $H_2$ (g). The reaction mixture was filtered through Celite and the filtrate was concentrated to yield **7** (0.50 g, 2.1 mmol, quant.) as a brown oil that was used directly without further purification; $R_f$ = 0.32 (hexane/EtOAc, 1:1).

HPLC purity: 99.0% (254 nm), 98.8% (220 nm); $t_R$ = 4.64 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.94 (s, 2 H), 5.06 (s, 2 H), 4.98 (s, 2 H), 3.60 (s, 3 H), 3.46 (s, 3 H), 3.37–3.70 (br s, 4 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 155.2, 140.8, 128.8, 99.7, 95.0, 94.8, 57.7, 56.1.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{17}N_2O_4^+$: 229.1; found: 229.1.

### *N*-[3-Amino-2,5-bis(methoxymethoxy)phenyl]-2-methyl-3-oxohexanamide (7a)

EDC·HCl (589 mg, 3.07 mmol) was added to a stirred solution of **7** (1.0 g, 4.38 mmol), 2-methyl-3-oxohexanoic acid (442 mg, 3.07 mmol), and DMAP (107 mg, 0.88 mmol) in $CH_2Cl_2$ (30 mL). The solution was stirred at r.t. for 30 min. The reaction mixture was diluted with $CH_2Cl_2$ (200 mL) and the organic layer was washed with $H_2O$ (2 × 100 mL). The organic layer was dried (anhyd $Na_2SO_4$), filtered, and concentrated to yield an oil that was purified by flash chromatography (NH-functionalized silica gel, hexane/EtOAc 9:1 to 5:2, v/v), affording **7a** (270 mg, 0.76 mmol, 25%) as a light brown oil as a pair of enantiomers; $R_f$ = 0.35 (hexane/EtOAc, 1:1).

HPLC purity: 97.0% (254 nm), 94.0% (220 nm); $t_R$ = 6.17 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.79 (br s, 1 H), 7.47 (d, *J* = 2.69 Hz, 1 H), 6.23 (d, *J* = 2.69 Hz, 1 H), 5.11 (s, 2 H), 5.01 (d, *J* = 5.62 Hz, 1 H), 4.96 (d, *J* = 5.62 Hz, 1 H), 3.92 (br s, 2 H), 3.63 (s, 3 H), 3.55 (q, *J* = 7.34 Hz, 1 H), 3.46 (s, 3 H), 2.51–2.66 (m, 2 H), 1.57–1.67 (m, 2 H), 1.48 (d, *J* = 7.34 Hz, 3 H), 0.91 (t, *J* = 7.34 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.3, 167.6, 154.7, 140.3, 132.4, 130.3, 100.4, 100.0, 99.1, 94.9, 58.0, 56.3, 56.1, 43.6, 17.1, 15.0, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{27}N_2O_6^+$: 355.1864; found: 355.1853; *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{26}N_2O_6Na^+$: 377.1683; found: 377.1671.

## Di-β-ketoanilides 9a–k

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(3-oxobutanamide) (9a)

A solution of 2,5-bis(methoxymethoxy)benzene-1,3-diamine (**7**; 150 mg, 0.66 mmol) in methyl acetoacetate (**8a**; 2.0 mL) was refluxed at 170 °C for 3 h. The reaction was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 2:3, v/v), affording **9a** (126 mg, 0.32 mmol, 48%) as an off-white solid; mp 89–90 °C; $R_f$ = 0.38 (hexane/EtOAc, 1:1).

HPLC purity: 99.3% (254 nm), 99.8% (220 nm); $t_R$ = 5.63 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 2 H), 7.80 (s, 2 H), 5.15 (s, 2 H), 5.07 (s, 2 H), 3.65 (s, 3 H), 3.58 (s, 4 H), 3.47 (s, 3 H), 2.34 (s, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 204.2, 163.6, 154.2, 132.4, 131.8, 105.0, 101.3, 95.0, 58.4, 56.4, 51.3, 31.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_8^+$: 397.1605; found: 397.1610; *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}N_2O_8Na^+$: 419.1425; found: 419.1424.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(3-oxohexanamide) (9b)

A solution of **7** (100 mg, 0.44 mmol) in methyl 3-oxohexanoate (**8b**; 1.2 mL) was refluxed at 190 °C for 1.5 h. The reaction was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 1:1, v/v), affording **9b** (75 mg, 0.17 mmol, 39%) as a light brown solid; mp 97–98 °C; $R_f$ = 0.33 (hexane/EtOAc, 1:1).

HPLC purity: 97.0% (254 nm), 95.4% (220 nm); $t_R$ = 6.58 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 2 H), 7.80 (s, 2 H), 5.15 (s, 2 H), 5.08 (s, 2 H), 3.67 (s, 3 H), 3.55 (s, 4 H), 3.47 (s, 3 H), 2.58 (t, *J* = 7.15 Hz, 4 H), 1.61–1.71 (m, 4 H), 0.95 (t, *J* = 7.34 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.5, 163.7, 154.2, 132.5, 131.9, 105.0, 101.4, 95.0, 58.4, 56.4, 50.6, 46.0, 17.1, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{33}N_2O_8^+$: 453.2231; found: 453.2227; *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{32}N_2O_8Na^+$: 475.2051; found: 475.2040.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(2-methyl-3-oxobutanamide) (9c)

A solution of **7** (100 mg, 0.44 mmol) in ethyl 2-methyl-3-oxobutanoate (**8c**; 2.0 mL) was stirred at 130 °C for 5 h. The reaction was cooled to r.t. and purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 1:1, v/v), affording **9c** (86 mg, 0.20 mmol, 46%) as an off-white solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*); mp 108–109 °C; $R_f$ = 0.25 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.03 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.90 (br. s, 4 H), 7.81 (s, 4 H), 5.16 (s, 4 H), 5.05 (d, *J* = 5.87 Hz, 1 H), 5.01 (s, 2 H), 4.97 (d, *J* = 5.87 Hz, 1 H), 3.67 (s, 6 H), 3.55 (q, *J* = 7.21 Hz, 4 H), 3.47 (s, 6 H), 2.31 (s, 12 H), 1.51 (d, *J* = 7.21 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 207.5, 167.5, 154.3, 132.4, 131.8, 104.8, 101.5, 95.0, 58.3, 56.4, 56.3, 28.9, 15.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_8^+$: 425.1918; found: 425.1916; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_8Na^+$: 447.1738; found: 447.1733.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(2-methyl-3-oxohexanamide) (9d)

A solution of **7** (400 mg, 1.75 mmol) in methyl 2-methyl-3-oxohexanoate (**8d**; 6.0 mL) was stirred at 210 °C for 1 h. The reaction mixture was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 3:2, v/v), affording **9d** (625 mg, 1.30 mmol, 74%) as an off-white solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*); mp 67–68 °C; $R_f$ = 0.39 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.95 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.91 (br s, 4 H), 7.80 (s, 4 H), 5.15 (s, 4 H), 5.08 (d, *J* = 5.87 Hz, 1 H), 5.01 (s, 2 H), 4.94 (d, *J* = 5.87 Hz, 1 H), 3.67 (s, 6 H), 3.53–3.60 (m, 4 H), 3.47 (s, 6 H), 2.56–2.61 (m, 8 H), 1.57–1.68 (m, 8 H), 1.49 (d, *J* = 7.34 Hz, 12 H), 0.92 (t, *J* = 7.34 Hz, 12 H).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.63 (s, 4 H), 7.39 (s, 4 H), 5.10 (s, 4 H), 4.91 (s, 4 H), 3.85 (q, *J* = 7.09 Hz, 4 H), 3.49 (s, 6 H), 3.36 (s, 6 H), 2.51–2.56 (m, 8 H), 1.43–1.55 (m, 8 H), 1.23 (d, *J* = 6.85 Hz, 12 H), 0.83 (t, *J* = 7.46 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.71, 209.69, 167.7, 154.3, 132.4, 131.9, 104.7, 101.4, 95.0, 58.4, 56.4, 55.8, 43.7, 43.6, 17.1, 15.3, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{37}N_2O_8^+$: 481.2544; found: 481.2538; *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{36}N_2O_8Na^+$: 503.2364; found: 503.2357.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(2-ethyl-3-oxobutanamide) (9e)

A solution of **7** (120 mg, 0.53 mmol) in ethyl 2-ethyl-3-oxobutanoate (**8e**; 2.0 mL) was stirred at 130 °C for 5 h. The reaction mixture was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 3:2, v/v), affording **9e** (165 mg, 0.37 mmol, 69%) as a white solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*); mp 122–123 °C; $R_f$ = 0.33 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.47 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 2 H), 8.93 (s, 2 H), 7.81 (s, 4 H), 5.15 (s, 4 H), 5.12 (d, *J* = 5.87 Hz, 1 H), 5.01 (s, 2 H), 4.90 (d, *J* = 5.87 Hz, 1 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 3.47 (s, 6 H), 3.39–3.45 (m, 4 H), 2.30 (s, 12 H), 1.93–2.04 (m, 8 H), 1.00 (t, *J* = 7.46 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 207.5, 207.4, 166.8, 154.3, 132.4, 132.3, 131.83, 131.82, 104.7, 104.6, 101.5, 101.4, 95.0, 64.12, 64.09, 58.4, 56.4, 29.9, 29.8, 24.4, 24.3, 12.1, 12.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{33}N_2O_8^+$: 453.2231; found: 453.2226; *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{32}N_2O_8Na^+$: 475.2051; found: 475.2041.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(4-methyl-3-oxopentanamide) (9f)

A solution of **7** (110 mg, 0.48 mmol) in ethyl 4-methyl-3-oxopentanoate (**8f**; 2.0 mL) was stirred at 130 °C for 5 h. The reaction mixture was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 5:2, v/v), affording **9f** (129 mg, 0.29 mmol, 60%) as a light brown solid; mp 68–69 °C; $R_f$ = 0.38 (hexane/EtOAc, 1:1).

HPLC purity: 99.3% (254 nm), 99.0% (220 nm); $t_R$ = 6.49 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.44 (br s, 2 H), 7.80 (s, 2 H), 5.15 (s, 2 H), 5.08 (s, 2 H), 3.67 (s, 3 H), 3.61 (s, 4 H), 3.47 (s, 3 H), 2.70–2.82 (m, 2 H), 1.17 (d, *J* = 7.09 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 210.2, 163.9, 154.1, 132.4, 131.9, 104.9, 101.3, 95.0, 58.5, 56.4, 48.4, 42.3, 18.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{33}N_2O_8^+$: 453.2231; found: 453.2231; *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{32}N_2O_8Na^+$: 475.2051; found: 475.2047.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(2-acetyl-3-methylbutanamide) (9g)

A solution of **7** (100 mg, 0.44 mmol) in ethyl 2-acetyl-3-methylbutanoate (**8g**; 2.0 mL) was stirred at 160 °C for 5 h. The reaction mixture was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 3:2, v/v), affording **9g** (150 mg, 0.31 mmol, 71%) as a light brown solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*); mp 125–126 °C; $R_f$ = 0.37 (hexane/EtOAc, 1:1).

HPLC purity: 95.0% (254 nm), 94.9% (220 nm); $t_R$ = 6.85 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.87 (br s, 2 H), 8.85 (br s, 2 H), 7.80 (s, 2 H), 7.79 (s, 2 H), 5.18 (d, *J* = 5.75 Hz, 1 H), 5.15 (s, 4 H), 4.99 (s, 2 H), 4.80 (d, *J* = 5.75 Hz, 1 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.47 (s, 6 H), 3.24 (d, *J* = 9.66 Hz, 2 H), 3.22 (d, *J* = 9.66 Hz, 2 H), 2.35–2.48 (m, 4 H), 2.32 (s, 6 H), 2.31 (s, 6 H), 1.03 (d, *J* = 6.60 Hz, 12 H), 0.99 (d, *J* = 6.60 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 208.1, 207.9, 166.12, 166.09, 154.3, 154.2, 132.3, 132.2, 131.9, 131.8, 104.6, 104.4, 101.5, 101.4, 95.0, 70.97, 70.89, 58.5, 58.4, 56.4, 31.7, 31.6, 31.3, 31.0, 21.02, 20.98, 20.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{37}N_2O_8^+$: 481.2544; found: 481.2533; *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{36}N_2O_8Na^+$: 503.2364; found: 503.2353.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(3-cyclopropyl-3-oxopropanamide) (9h)

A solution of **7** (150 mg, 0.66 mmol) in ethyl 3-cyclopropyl-3-oxopropanoate (**8h**; 2.0 mL) was stirred at 160 °C for 1 h. The reaction mixture was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 1:1, v/v), affording **9h** (210 mg, 0.47 mmol, 71%) as a white solid; mp 123–124 °C; $R_f$ = 0.38 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.21 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 2 H), 7.81 (s, 2 H), 5.15 (s, 2 H), 5.02 (s, 2 H), 3.69 (s, 4 H), 3.61 (s, 3 H), 3.46 (s, 3 H), 2.01–2.13 (m, 2 H), 1.13–1.20 (m, 4 H), 0.98–1.07 (m, 4 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.5, 163.9, 154.1, 132.4, 131.9, 105.0, 101.3, 95.0, 58.4, 56.4, 50.7, 21.9, 12.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}N_2O_8^+$: 449.1918; found: 449.1917; *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{28}N_2O_8Na^+$: 471.1738; found: 471.1732.

### *N*,*N*′-[2,5-Bis(methoxymethoxy)-1,3-phenylene]bis(2-benzyl-3-oxobutanamide) (9i)

A solution of **7** (150 mg, 0.66 mmol) in ethyl 2-benzyl-3-oxobutanoate **8i** (2.0 mL) was stirred at 170 °C for 1 h. The reaction mixture was cooled to r.t. and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 1:1, v/v), affording **9i** (90 mg, 0.16 mmol, 24%) as a brown oil as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*); $R_f$ = 0.47 (hexane/EtOAc, 1:1).

HPLC purity: 99.9% (254 nm), 98.9% (220 nm); $t_R$ = 7.07 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 4 H), 7.78 (s, 4 H), 7.17–7.32 (m, 20 H), 5.16 (s, 4 H), 4.81 (d, *J* = 5.87 Hz, 1 H), 4.73 (s, 2 H), 4.66 (d, *J* = 5.87 Hz, 1 H), 3.74–3.80 (m, 4 H), 3.56 (s, 3 H), 3.55 (s, 3 H), 3.49 (s, 6 H), 3.18–3.34 (m, 8 H), 2.18 (s, 6 H), 2.17 (s, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.6, 166.2, 154.3, 137.7, 132.5, 131.6, 129.0, 127.2, 104.93, 104.90, 101.24, 101.18, 95.0, 64.4, 64.3, 58.2, 56.5, 36.9, 36.8, 30.4, 30.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{37}N_2O_8^+$: 577.2544; found: 577.2523; *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{36}N_2O_8Na^+$: 599.2364; found: 599.2342.

### *N*-[2,5-Bis(methoxymethoxy)-3-(3-oxobutanamido)phenyl]-2-methyl-3-oxohexanamide (9j)

EDC·HCl (108 mg, 0.56 mmol) was added to a stirred solution of **7a** (100 mg, 0.28 mmol), 3-oxobutanoic acid (**8j**; 58 mg, 0.56 mmol), and DMAP (6.8 mg, 0.056 mmol) in $CH_2Cl_2$ (5 mL). The solution was stirred at r.t. for 30 min. The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) and the organic layer was washed with $H_2O$ (2 × 25 mL). The

organic layer was dried (anhyd $Na_2SO_4$), filtered, and concentrated to yield an oil that was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 3:2, v/v), affording **9j** (105 mg, 0.24 mmol, 86%) as a light brown solid as a pair of enantiomers; mp 80–81 °C; $R_f$ = 0.25 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.34 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 8.92 (s, 1 H), 7.82 (d, *J* = 2.93 Hz, 1 H), 7.78 (d, *J* = 2.93 Hz, 1 H), 5.15 (s, 2 H), 5.08 (d, *J* = 5.87 Hz, 1 H), 5.01 (d, *J* = 5.87 Hz, 1 H), 3.67 (s, 3 H), 3.60 (s, 2 H), 3.55 (q, *J* = 7.09 Hz, 1 H), 3.47 (s, 3 H), 2.52–2.66 (m, 2 H), 2.33 (s, 3 H), 1.57–1.68 (m, 2 H), 1.48 (d, *J* = 7.09 Hz, 3 H), 0.91 (t, *J* = 7.34 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.2, 204.7, 167.8, 163.6, 154.2, 132.4, 131.9, 131.8, 104.9, 104.7, 101.4, 94.9, 58.4, 56.4, 56.0, 50.8, 43.5, 31.3, 17.1, 15.0, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{31}N_2O_8^+$: 439.2075; found: 439.2071; *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{30}N_2O_8Na^+$: 461.1894; found: 461.1891.

### *N*-[2,5-Bis(methoxymethoxy)-3-(2-methyl-3-oxobutanamido)-phenyl]-2-methyl-3-oxohexanamide (9k)

EDC·HCl (65 mg, 0.34 mmol) was added to a stirred solution of **7a** (60 mg, 0.17 mmol), 2-methyl-3-oxobutanoic acid (**8k**; 39 mg, 0.34 mmol), and DMAP (4.0 mg, 0.034 mmol) in $CH_2Cl_2$ (2 mL). The solution was stirred at r.t. for 30 min. The reaction mixture was diluted with $CH_2Cl_2$ (30 mL) and the organic layer was washed with $H_2O$ (2 × 15 mL). The organic layer was dried (anhyd $Na_2SO_4$), filtered, and concentrated to yield an oil that was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 3:2, v/v), affording **9k** (60 mg, 0.13 mmol, 78%) as a light brown solid as a mixture of two pairs of enantiomers (*R*,*R*; *S*,*S* and *S*,*R*; *R*,*S*); mp 82–83 °C; $R_f$ = 0.29 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 100.0% (220 nm); $t_R$ = 6.52 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 2 H), 8.89 (br s, 2 H), 7.80 (s, 4 H), 5.15 (s, 4 H), 5.07 (d, *J* = 5.62 Hz, 1 H), 5.04 (d, *J* = 5.62 Hz, 1 H), 4.99 (d, *J* = 5.62 Hz, 1 H), 4.95 (d, *J* = 5.62 Hz, 1 H), 3.67 (s, 6 H), 3.50–3.60 (m, 4 H), 3.47 (s, 6 H), 2.59 (t, *J* = 7.15 Hz, 2 H), 2.59 (t, *J* = 7.15 Hz, 2 H), 2.30 (s, 6 H), 1.57–1.68 (m, 4 H), 1.50 (d, *J* = 7.30 Hz, 6 H), 1.49 (d, *J* = 7.30 Hz, 6 H), 0.92 (t, *J* = 7.46 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.9, 207.3, 167.7, 167.6, 167.5, 154.3, 132.4, 131.9, 131.8, 104.73, 104.67, 101.4, 94.9, 58.3, 56.41, 56.36, 55.7, 43.8, 43.7, 28.84, 28.76, 17.1, 15.5, 15.4, 14.9, 14.8, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{33}N_2O_8^+$: 453.2231; found: 453.2234; *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{32}N_2O_8Na^+$: 475.2051; found: 475.2050.

### Substrates 10–16; General Procedure

The di-β-ketoanilides **10**–**16** were prepared from their corresponding diamines via 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) coupling with 2-methyl-3-oxohexanoic acid in $H_2O$ or $CH_2Cl_2$ (Schemes S1–S7, Supporting Information).

### *N*,*N*′-(5-Hydroxy-1,3-phenylene)bis(2-methyl-3-oxohexanamide) (10)

Yield: 350 mg (57%) (1.63 mmol scale); $CH_2Cl_2$ was used as the solvent to give **10** as an off-white solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*) after flash column chromatography (hexane/EtOAc 9:1 to 2:1, v/v); mp 62–63 °C; $R_f$ = 0.25 (hexane/EtOAc, 1:1).

HPLC purity: 100.0% (254 nm), 95.8% (220 nm); $t_R$ = 6.25 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.81 (br s, 2 H), 8.59 (br s, 1 H), 7.13 (s, 2 H), 7.05 (s, 1 H), 3.58 (q, *J* = 7.09 Hz, 2 H), 2.57 (t, *J* = 7.18 Hz, 4 H), 1.53–1.65 (m, 4 H), 1.45 (d, *J* = 7.09 Hz, 6 H), 0.88 (t, *J* = 7.28 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 210.5, 210.4, 169.12, 169.08, 158.0, 138.9, 104.2, 103.5, 54.8, 43.8, 17.0, 15.7, 15.6, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_5^+$: 377.2071; found: 377.2075; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_5Na^+$: 399.1890; found: 399.1889.

### *N*,*N*′-(2-Hydroxy-1,3-phenylene)bis(2-methyl-3-oxohexanamide) (11)

Yield: 325 mg (53%) (1.63 mmol scale); $H_2O$/1 M HCl (5:1) was used as the solvent to give **11** as a light brown oil as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*) after flash column chromatography (hexane/EtOAc 9:1 to 2:1, v/v); $R_f$ = 0.57 (hexane/EtOAc, 1:1).

HPLC purity: 97.8% (254 nm), 97.5% (220 nm); $t_R$ = 6.72 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.58 (s, 1 H), 9.07 (br s, 2 H), 7.45 (d, *J* = 8.07 Hz, 2 H), 6.86 (t, *J* = 8.07 Hz, 1 H), 3.62 (q, *J* = 7.34 Hz, 2 H), 2.61 (t, *J* = 7.21 Hz, 4 H), 1.60–1.71 (m, 4 H), 1.53 (d, *J* = 7.34 Hz, 6 H), 0.93 (t, *J* = 7.46 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 210.2, 169.3, 138.5, 127.5, 120.7, 117.7, 54.2, 44.0, 17.0, 16.2, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_5^+$: 377.2071; found: 377.2072; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_5Na^+$: 399.1890; found: 399.1898.

### *N*,*N*′-(1,3-Phenylene)bis(2-methyl-3-oxohexanamide) (12)

Yield: 247 mg (75%) (0.92 mmol scale); $CH_2Cl_2$ was used as the solvent to give **12** as a viscous light brown oil as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*) after flash column chromatography (hexane/EtOAc 9:1 to 2:1, v/v); $R_f$ = 0.50 (hexane/EtOAc, 1:1).

HPLC purity: 96.2% (254 nm), 97.5% (220 nm), $t_R$ = 6.62 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.57 (s, 2 H), 7.75–7.79 (m, 1 H), 7.29–7.33 (m, 2 H), 7.21–7.26 (m, 1 H), 3.56 (q, *J* = 7.25 Hz, 2 H), 2.58 (t, *J* = 7.28 Hz, 4 H), 1.56–1.68 (m, 4 H), 1.47 (d, *J* = 7.34 Hz, 6 H), 0.91 (t, *J* = 7.46 Hz, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 210.5, 168.2, 138.4, 129.7, 116.2, 111.7, 55.0, 43.8, 17.0, 15.7, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_4^+$: 361.2122; found: 361.2117; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_4Na^+$: 383.1941; found: 383.1934.

### *N*,*N*′-(2-Hydroxy-1,4-phenylene)bis(2-methyl-3-oxohexanamide) (13)

Yield: 55 mg (96%) (0.15 mmol scale); $CH_2Cl_2$ was used as the solvent to give **13** as an off-white solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*); mp 143–144 °C; $R_f$ = 0.34 (hexane/EtOAc, 1:1).

HPLC purity: 96.8% (254 nm), 98.1% (220 nm); $t_R$ = 6.37 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.17 (br s, 1 H), 8.83 (s, 1 H), 8.69 (s, 1 H), 7.48–7.54 (m, 2 H), 6.84 (dd, *J* = 8.68, 2.32 Hz, 1 H), 3.54–3.65 (m, 2 H), 2.57–2.65 (m, 4 H), 1.58–1.70 (m, 4 H), 1.52 (d, *J* = 7.34 Hz, 3 H), 1.51 (d, *J* = 7.34 Hz, 3 H), 0.93 (t, *J* = 7.46 Hz, 3 H), 0.92 (t, *J* = 7.46 Hz, 3 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_5^+$: 377.2071; found: 377.2088; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_5Na^+$: 399.1890; found: 399.1913.

***N,N′*-(2-Methyl-1,3-phenylene)bis(2-methyl-3-oxohexanamide) (14)**

Yield: 230 mg (75%) (0.82 mmol scale); $H_2O$/1 M HCl (5:1) used as the solvent to give **14** as an off-white solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*) after filtration and washing with $H_2O$; mp 232–233 °C; $R_f$ = 0.30 (hexane/EtOAc, 1:1).

HPLC purity: 96.3% (254 nm), 98.9% (220 nm); $t_R$ = 6.45 min.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.73 (s, 2 H), 7.16 (s, 3 H), 3.73 (q, *J* = 6.91 Hz, 2 H), 2.56 (t, *J* = 7.09 Hz, 2 H), 2.56 (t, *J* = 7.09 Hz, 2 H), 2.04 (s, 3 H), 1.46–1.57 (m, 4 H), 1.24 (d, *J* = 6.85 Hz, 6 H), 0.85 (t, *J* = 7.46 Hz, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 206.4, 168.9, 136.5, 128.3, 125.4, 123.5, 53.3, 42.1, 16.6, 13.5, 13.1, 12.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{31}N_2O_4^+$: 375.2278; found: 375.2231; *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{30}N_2O_4Na^+$: 397.2098; found: 397.2047.

***N,N′*-(2,5-Dihydroxy-1,4-phenylene)bis(2-methyl-3-oxohexanamide) (15)**

Yield: 143 mg (78%) (0.47 mmol scale); $H_2O$ was used as the solvent to give **15** as a grey solid as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*) after filtration and washing with $H_2O$; mp 186–187 °C; $R_f$ = 0.25 (hexane/EtOAc, 1:1).

HPLC purity: 97.6% (254 nm), 98.2% (220 nm); $t_R$ = 6.24 min.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.39 (s, 2 H), 9.24 (s, 2 H), 7.50 (s, 2 H), 3.89 (q, *J* = 6.85 Hz, 2 H), 2.49–2.55 (m, 4 H), 1.43–1.52 (m, 4 H), 1.19 (d, *J* = 6.85 Hz, 6 H), 0.82 (t, *J* = 7.34 Hz, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 206.8, 168.7, 139.7, 122.0, 109.1, 53.5, 42.1, 16.6, 13.5, 13.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_6^+$: 393.2020; found: 393.2038; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}N_2O_6Na^+$: 415.1840; found: 415.1859.

***N,N′*-(2,5-Dioxocyclohexa-3,6-diene-1,3-diyl)bis(2-methyl-3-oxohexanamide) (16)**

DDQ (11 mg, 0.048 mmol) was added to a solution of **1d** (19 mg, 0.048 mmol) in $CH_2Cl_2$ (2 mL) and stirred at r.t. for 30 min. The reaction mixture was filtered and the filtrate was concentrated in vacuo to yield an oil that was purified by flash chromatography (silica gel, hexane/EtOAc 9:1 to 3:2, v/v) affording **16** (15 mg, 0.038 mmol, 80%) as an orange oil as a mixture of enantiomers (*R*,*R* and *S*,*S*) and *meso* form (*S*,*R* = *R*,*S*); $R_f$ = 0.57 (hexane/EtOAc, 1:1).

HPLC purity: 91.4% (254 nm), 100.0% (220 nm); $t_R$ = 6.80 min.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.39 (s, 2 H), 9.38 (s, 2 H), 7.48 (s, 4 H), 3.62 (q, *J* = 7.34 Hz, 4 H), 2.58 (t, *J* = 7.21 Hz, 8 H), 1.58–1.69 (m, 8 H), 1.50 (d, *J* = 7.34 Hz, 12 H), 0.92 (t, *J* = 7.46 Hz, 12 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.72, 209.69, 188.7, 179.2, 169.11, 169.09, 136.5, 116.4, 54.7, 44.2, 44.1, 16.9, 16.02, 15.96, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}N_2O_6^+$: 391.1864; found: 391.1866; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2O_6Na^+$: 413.1683; found: 413.1690.

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## Supporting Information

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