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Formal synthesis of salinosporamide A via NHC-catalyzed intramolecular lactonization

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Dedicated to Professor Michael Krische in honor of his 2008 Tetrahedron Young Investigator Award

ABSTRACT

An *N*-heterocyclic carbene (NHC) catalyzed intramolecular lactonization to prepare densely functionalized bicyclic γ-lactam-γ-lactone adducts from enals is reported. This method has been applied to the formal synthesis of salinosporamide A, a potent 20S proteasome inhibitor and anti-cancer therapeutic.

1. Introduction

Over the past decade, significant advances have been achieved in reactions catalyzed by *N*-heterocyclic carbenes (NHCs).[1] Conceptually new reaction pathways have been identified, making possible the production of stereochemically rich heterocycles from simple, readily available starting materials under exceptionally mild reaction conditions. An intriguing feature of these reactions is the often exquisite control over competing reaction pathways. For example, α,β-unsaturated enals can react as either homoenolate or ester enolate equivalents (Fig. 1). In intermolecular annulation reactions, we have been successful in achieving complete control over these reaction pathways through careful choice of catalysts and reaction conditions.[2]

To further explore the ability of catalyst design to dictate the reaction outcome, we wished to examine the more challenging case of selective enolate versus homoenolate reactivity in a densely functionalized substrate that would lead to synthetically valuable bicyclic products. In this article, we document our studies on asymmetric intramolecular cyclizations catalyzed by *N*-heterocyclic carbenes and its application to a formal synthesis of salinosporamide A.

These studies originate from our recent discovery that α,β-unsaturated aldehydes undergo reactions with *N*-heterocyclic carbenes, leading to the catalytic generation of homoenolates or enolates via internal redox processes.[3] We have applied the generation of homoenolates to the formation of γ-lactones[2a] and γ-lactams.[4] We have also disclosed that enals and α-chloroaldehydes serve as precursors to ester enolate equivalents for highly enantioselective inverse electron demand Diels–Alder reactions.[5] Building on these studies, Scheidt has reported intramolecular variants of both the homoenolate and enolate pathways and has alluded to competition between these two reaction manifolds in cyclization reactions.[6]

We recognized that an intramolecular cyclization via the homoenolate pathway would provide a concise entry into the salinosporamide class of natural products (Fig. 2). Salinosporamide A[7] is a secondary metabolite of the marine actinomycete bacteria of Salinospora strain CNB-392. It is a potent inhibitor of the 20S proteasome and has attracted much attention[8] because of its impressive in vitro cytotoxic activity against many tumor cell lines. In order to execute this synthesis, however, we needed to identify catalysts and reaction conditions that would react selectively via the desired homoenolate pathway.

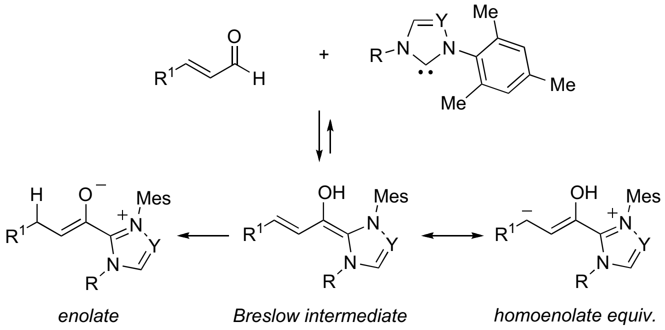

Figure 1. Reactive intermediates formed between NHCs and enals.

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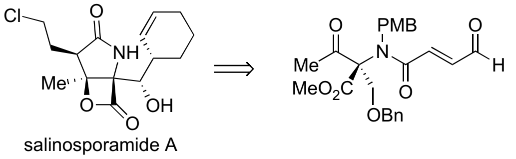


Figure 2.

2. Results and discussion

2.1. Development of an NHC-catalyzed intramolecular cyclization–lactonization

We sought to develop a general strategy toward the formation of *cis*-fused γ-lactam-γ-lactone adducts via an NHC-promoted intramolecular homoenolate addition of an enal to a tethered ketone followed by lactonization of the resulting alkoxide on the subsequently formed activated carboxylate (Fig. 3).

Toward this end, aldehyde **1** was synthesized by the coupling of **2**[9] and acid **3** (Scheme 1). However, when **1** was allowed to react with commercially available NHC precatalyst IMesCl or RMesCl[10] in THF at 40 °C in the presence of DBU, the desired product was not observed but rather the *N*-substituted succinimide **4** was obtained exclusively via NHC-catalyzed redox generation of the activated carboxylate (Scheme 1).

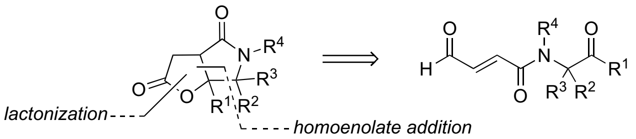
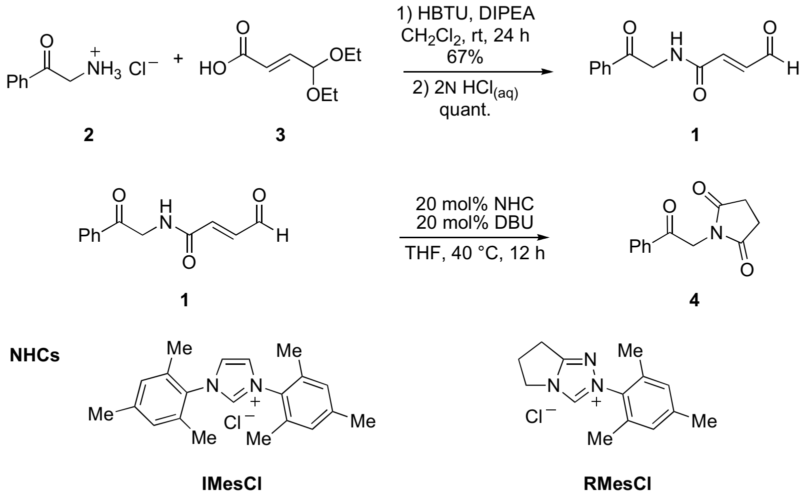


Figure 3. Retrosynthetic strategy toward γ-lactam-γ-lactone adducts.

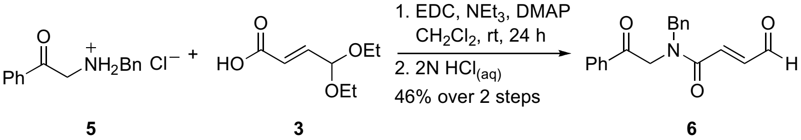
At this point we recognized the need to employ a protecting group on the amide prior to cyclization. The benzyl protecting group was chosen based on ease of the preparation of the amine coupling partner as well as the potential for its facile removal by catalytic hydrogenation. *N*-Benzyl protected phenyl ketone **5** was synthesized from 2-bromoacetophenone and subsequently coupled with acid **3** using EDC. Deprotection of the acetal using aqueous hydrochloric acid afforded the aldehyde **6** (Scheme 2). We subjected the aldehyde to NHC-precatalyst RMesCl with DBU in THF at 40 °C and were pleased to find the desired product, albeit in low yield and as a complex mixture.

Careful analysis of the reaction mixture revealed that in addition to the desired γ-lactam-γ-lactone product **7**, six-membered lactam **8** was also formed. A plausible catalytic cycle is presented in Figure 4. Deprotonation of the precatalyst provides the active NHC catalyst that undergoes nucleophilc attack on the enal. A proton transfer event leads to the Breslow intermediate, the fate of which is intimately related to the strength of base and reaction conditions employed. A resonance structure of the Breslow intermediate is the homoenolate equivalent; this can participate in an intramolecular nucleophilic addition to the ketone followed by lactonization via the resultant activated carboxylate to turn the catalyst over and produce the desired lactam **7** (pathway A). Protonation of the homoenolate, however, renders an NHC-enolate that can undergo an intramolecular keto–aldol addition. Lactonization would then result in expulsion of the catalyst and formation β-lactone **9**, which readily undergoes decarboxylation[11] to δ-lactam **8** (pathway B). From the reaction mixture, we also isolated **10**, which we believe arises from a base-catalyzed olefin isomerization, followed by an intramolecular aldol addition (aldol pathway C). We corroborated pathway C by subjecting aldehyde **6** to DBU in THF at 40 °C; complete conversion to the α-pyridone **10** was observed (Scheme 3).

Optimization was carried out in an attempt to bias the formation of the desired γ-lactam-γ-lactone, which arises from pathway A. The most pertinent results are summarized in Table 1. When imidazolium catalyst IMesCl was used in conjunction with strong tertiary amine base DBU, the intramolecular aldol pathway C predominated (entry 1). However, when a weaker tertiary amine base was employed, pathway C was completely suppressed but the formation of products arising from the enolate pathway B increased (entry 3). We attribute this to the facile protonation of the homoenolate by the conjugate acid of triethylamine. Use of the triazolium catalyst RMesCl yielded products of all three pathways with pathway B dominating when DBU was used (entry 2), and pathways A and B dominating when the weaker amine base triethylamine was used (entry 4). We further discovered that of the chiral triazolium NHC-precatalysts tested, pathway C could be suppressed when catalyst **12**, reported by Scheidt and coworkers,[12] was used along with either a strong base under dilution (entry 5), a bulky tertiary amine base in a chlorinated solvent (entry 6) or strong base in *t*-BuOH (entry 7). However, we could never bias the product distribution to favor the desired γ-lactam-γ-lactone product in greater than 50% yield.



Scheme 1. Initially attempted NHC-catalyzed intramolecular cyclization (HBTU=*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DIPEA=*N*,*N*-diisopropylethylamine, DBU=1,8-diazabicyclo[5.4.0]undec-7-ene).



Scheme 2. Synthesis of benzyl protected substrate **6** (Bn=benzyl, EDC=*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, DMAP=4-(dimethylamino)pyridine).

From these results we hypothesized that there may exist a rotational barrier for the two rotamers of tertiary amide. As such, one rotamer might undergo intramolecular cyclization by the homoenolate faster than the other. The rate of this rotation might be in competition with the rate of protonation of the homoenolate that leads to the enolate, which cyclizes to form the products of pathway B. To test this hypothesis, we subjected **6** to our optimized conditions at 60 °C and indeed a more favorable product distribution was achieved (entries 8 and 9). However, further increase in temperature did not improve the ratio of desired product (entry 10).

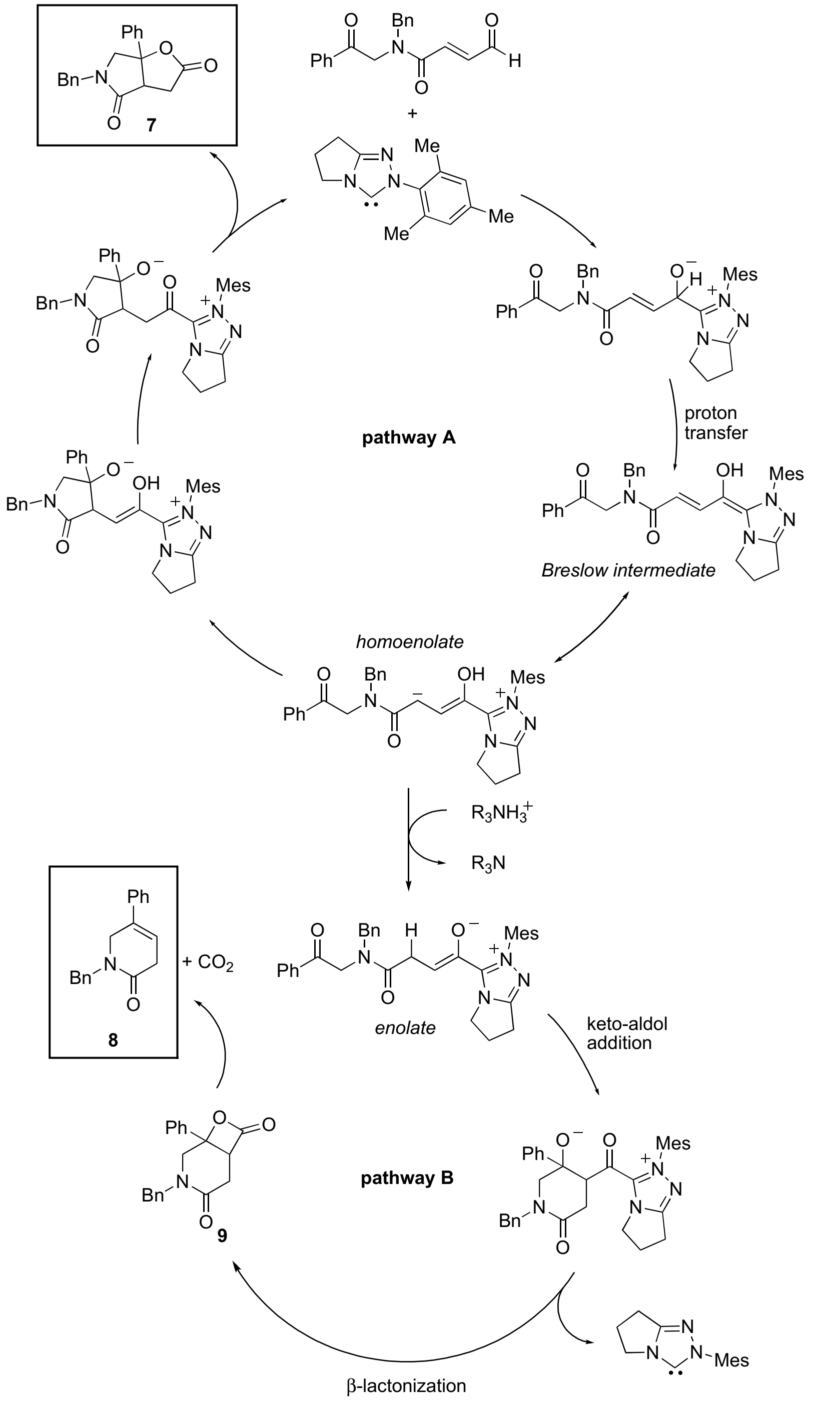
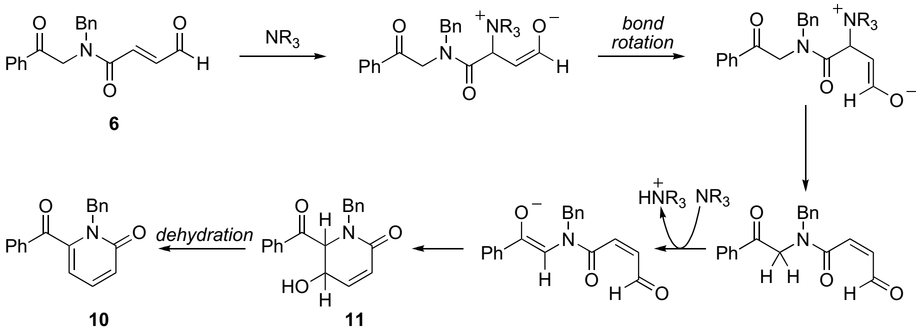
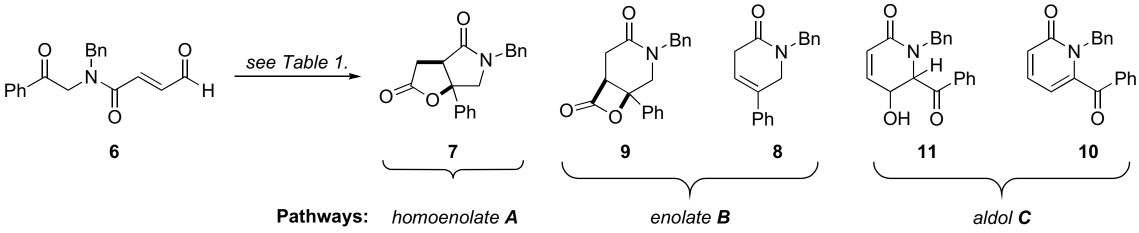


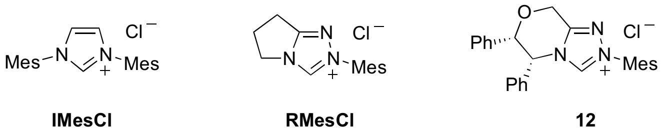
Figure 4. Postulated catalytic cycles for NHC-promoted pathways A and B (Mes=2,4,6-trimethylphenyl).



Scheme 3. Base catalyzed intramolecular aldol pathway C.

Table 1
NHC-catalyzed cyclization–lactonization of substrate **6**



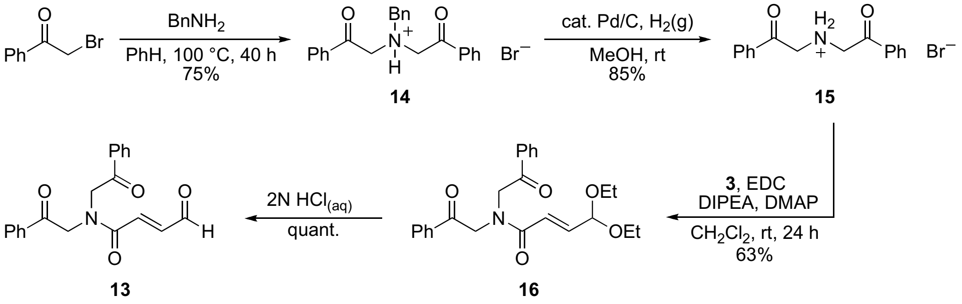


Entry	Catalyst (mol %)	Base (mol %)	Solvent (concn)	Temp (°C)	A/B/C[a]
1	IMesCl (20)	DBU (15)	THF (0.1 M)	40	1:—:10
2	RMesCl (20)	DBU (15)	THF (0.1 M)	40	1:1:2
3	IMesCl (20)	NEt_3 (15)	THF (0.1 M)	40	2.5:2:—
4	RMesCl (20)	NEt_3 (15)	THF (0.1 M)	40	2.5:2.5:1
5	**12** (15)	DBU (10)	10:1 THF/*t*-BuOH (0.02 M)	40	1:1:—
6	**12** (15)	DIPEA (100)	CH_2Cl_2 (0.1 M)	40	1:1:v
7	**12** (15)	DBU (10)	*t*-BuOH (0.1 M)	40	6.2:5.3:1
8	**12** (15)	DBU (10)	*t*-BuOH (0.1 M)	60	1.4:1:—
9	**12** (15)	NEt_3 (10)	*t*-BuOH (0.1 M)	60	1.6:1:—
10	**12** (15)	DBU (10)	*t*-BuOH (0.1 M)	80	1.4:1:—

All reactions listed proceeded with 100% conversion; isolated yields were not determined.

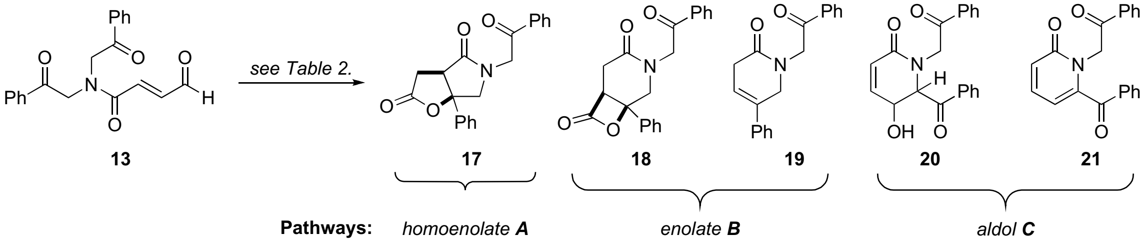
[a] Product pathway ratios determined from ^{1}H NMR analysis of unpurified reaction mixtures.

Similarly, we reasoned that a symmetrical tertiary amide would obviate the need for elevated temperatures to bias the homoenolate pathway A. Aldehyde **13** was synthesized to further probe our initial hypothesis (Scheme 4). The symmetrical bisketone **15** was synthesized in two steps from 2-bromoacetophenone and subsequently coupled with acid **3** using EDC. Deprotection of the diethyl acetal with aqueous hydrochloric acid furnished the symmetrical α,β-unsaturated aldehyde **13**.



Scheme 4. Synthesis of symmetrical substrate enal **13** (Bn=benzyl, EDC=*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, DIPEA=*N*,*N*-diisopropylethylamine, DMAP=4-(dimethylamino)pyridine).

Table 2
NHC-catalyzed cyclization–lactonization of substrate **13**



Entry	Catalyst (mol %)	Base (mol %)	Solvent (concn)	Temp (°C)	A/B/C[a]
1	RMesCl (15)	DBU (10)	*t*-BuOH (0.1 M)	60	3:1:2
2	IMesCl (15)	DBU (10)	*t*-BuOH (0.1 M)	60	1:1.5:8
3	**12** (15)	DBU (10)	*t*-BuOH (0.1 M)	60	4:1:1
4	RMesCl (15)	DBU (10)	10:1 THF/*t*-BuOH (0.10 M)	60	1:1.5:—
5	RMesCl (15)	DBU (10)	10:1 THF/*t*-BuOH (0.10 M)	40	1:1.3:—
6	RMesCl (15%)	DIPEA (10%)	10:1 THF/*t*-BuOH (0.10 M)	40	1:1.2:—
7	RMesCl (15)	*t*-BuOK (10)	10:1 THF/*t*-BuOH (0.10 M)	40	1:1:1
8	RMesCl (15)	DBU (10)	10:1 THF/*t*-BuOH (0.10 M)	20	1:—:6.7
9	RMesCl (15)	DBU (10)	10:1 THF/*t*-BuOH (0.05 M)	40	4:1:1
10	RMesCl (15)	DIPEA (10)	10:1 THF/*t*-BuOH (0.05 M)	40	1:1:trace
11	RMesCl (15)	DBU (50)	10:1 THF/*t*-BuOH (0.05 M)	40	1:—:10
12	RMesCl (15)	DIPEA (50)	10:1 THF/*t*-BuOH (0.05 M)	40	1:1:—
13	RMesCl (15)	DBU (10)	10:1 THF/*t*-BuOH (0.01 M)	40	3:1:trace

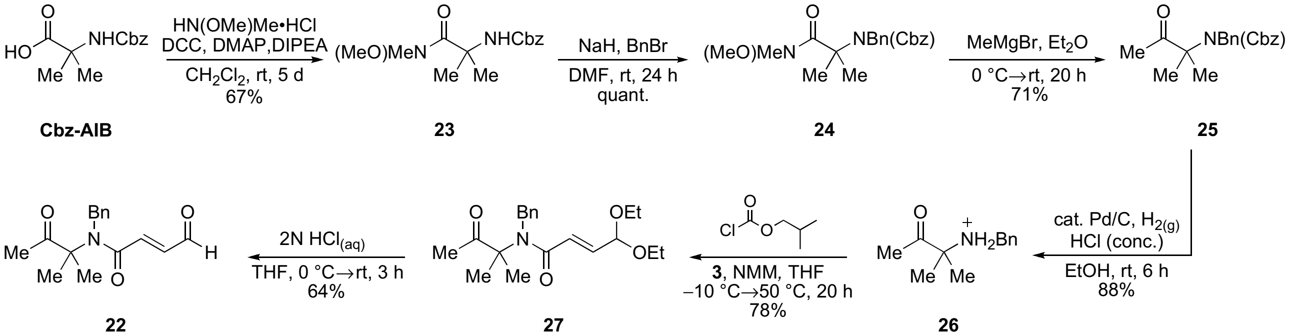
All reactions listed proceeded with 100% conversion; isolated yields were not determined.
[a] Product pathway ratios determined from ^{1}H NMR analysis of unpurified reaction mixtures.

Initially triazolium catalysts were identified as superior to imidazolium catalysts, such as IMesCl, for obtaining the desired γ-lactam-γ-lactone product **17** (Table 2, entries 1–3). Further optimization identified 10:1 THF/*t*-BuOH as the most suitable solvent system and RMesCl the best precatalyst for biasing pathway A (entries 4–13). It should be noted that strong bases DBU and *t*-BuOK (entries 4, 5, and 7) as well as the weaker but bulkier tertiary amine base DIPEA (entry 6) helped to suppress pathway C. Lowering the temperature initially suppressed pathway C (entries 4 and 5) but further cooling suppressed pathway B while enhancing pathway C (entry 8). Dilution favored pathway A (entries 9–13), whereas raising the amount of base tended to favor pathway C for the strong base DBU (entry 11) but pathway B for the weaker base DIPEA (entry 12). The optimal conditions identified employed DBU at lower loading than the catalyst, moderate heating (40 °C), and dilute (0.01 M), resulting in a 3:1 ratio of A/B (entry 13). Although we proved that the symmetrical substrate did provide a better ratio of the desired product, we could not easily purify **17** from **19**.

Of the two competing undesired pathways (B and C), pathway C was the easier to address. By blocking the α-position of the ketone, we could effectively eliminate pathway C since no enolizable hydrogens would exist. Also, there would be no concern for the use of either a strong base or an excess (compared to the precatalyst) of base. For this purpose, the geminal dimethyl substrate **22** was designed and synthesized (Scheme 5). Starting from Cbz-AIB, the acid was converted to the Weinreb amide **23** using DCC. N-Alkylation was carried out in DMF with NaH and benzyl bromide providing **24** in quantitative yield.

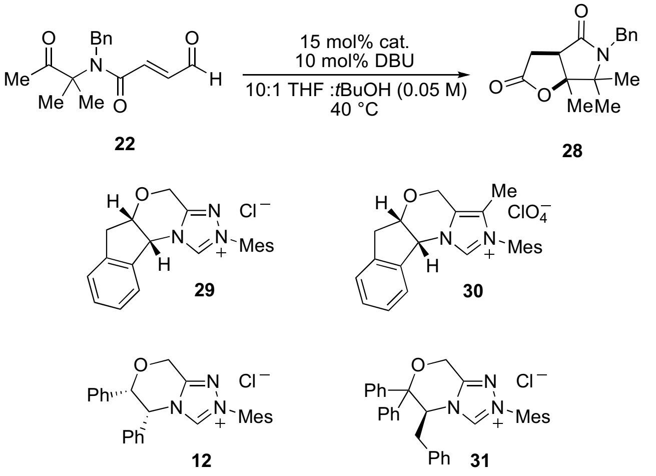
Formation of methyl ketone **25** was achieved using MeMgBr in Et_2O, and the benzyl carbamate was removed by catalytic hydrogenation in acidic media to give **26**. Amide formation with acid **3** proved most efficient via the isobutyl mixed anhydride at elevated temperature; standard coupling reagents such as HBTU, HATU, EDC were ineffective. Finally, deprotection of the diethyl acetal **27** afforded the desired aldehyde **22** in moderate yield due to its sensitivity to silica gel purification.

When aldehyde **22** was allowed to react in the presence of 15 mol % of RMesCl, 10 mol % of DBU at 0.05 M in 10:1 THF/*t*-BuOH for 20 h, we identified only the desired γ-lactam-γ-lactone **28**. We further identified that IMesCl was an even more effective catalyst for the desired transformation, providing the desired lactam in 79% isolated yield (Table 3, entry 1). We briefly screened several chiral precatalysts. Our triazolium *N*-mesityl aminoindanol-derived precatalyst **29** provided **28** in 75% yield but only 5% ee (entry 2). Our structurally related imidazolium *N*-mesityl aminoindanol-derived precatalyst **30** provided **28** in a reduced 50% yield and 9% ee (entry 3). Two chiral *N*-mesityl triazolium precatalysts, **12** and **31**, developed by Scheidt and co-workers[6a,12] proved just as effective with a slight



Scheme 5. Synthesis of *gem*-dimethyl substrate **22** (Cbz=benzyl carboxy, Bn=benzyl, DCC=*N*,*N*′-dicyclohexylcarbodiimide, DMAP=4-(dimethylamino)pyridine, DIPEA=*N*,*N*-diisopropylethylamine, NMM=*N*-methylmorpholine).

Table 3
NHC-catalyzed cyclization–lactonization of substrate **22**



Entry	Catalyst	Yield (%)	%ee[a]
1	IMesCl	79	—
2	**29**	75	5
3	**30**	50	9
4	**12**	78	9
5	**31**	73	23 (40)[b]

All reactions listed proceeded with 100% conversion.

[a] Determined by chiral SFC analysis.

[b] Performed at −20 °C.

increase in enantiomeric excess (entries 4 and 5). By employing precatalyst **31** and reducing the temperature to −20 °C, we obtained the γ-lactam-γ-lactone **28** with an enantiomeric excess of 40%.

Encouraged by our results we sought to apply our methodology to streamlining the previously reported synthesis of salinosporamide A. During the course of our investigation, Lam and coworkers reported a formal synthesis of salinosporamide A from **32** via a nickel-catalyzed reductive aldol cyclization–lactonization strategy to construct **33**.[8g] In parallel studies, we had identified intermediate **33** as a target for our NHC-promoted intramolecular cyclization–lactonization strategy (Fig. 5) for a formal synthesis of salinosporamide A. Our retrosynthetic plan is outlined in Figure 6. Lactam **33** would be obtained from the NHC catalyzed cyclization–lactonization of aldehyde **34**, which in turn would be synthesized in an analogous manner to our previous aldehyde substrates via amide bond formation between acid **3** and amine **36** followed by oxidation. The synthesis of **36** from L-threonine has previously been reported by Corey in his synthesis of salinosporamide A.[8a]

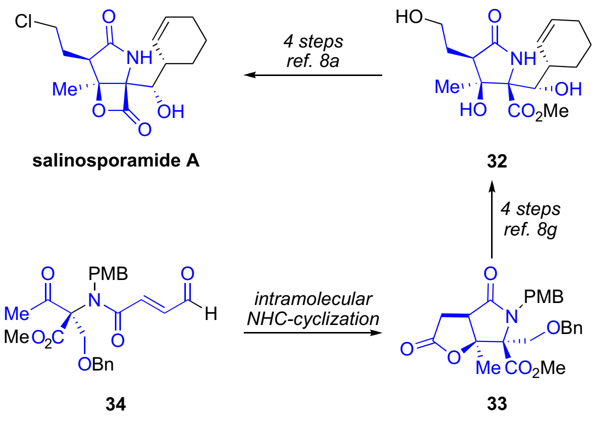


Figure 5. Proposed formal synthesis of salinosporamide A from aldehyde **34** employing our intramolecular NHC-cyclization.

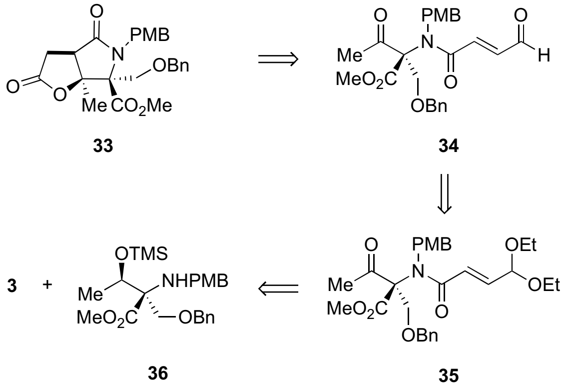
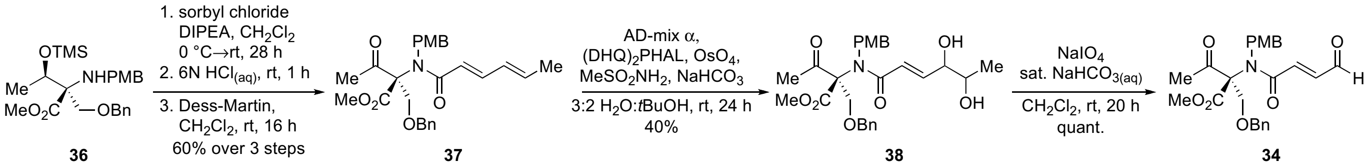


Figure 6. Retrosynthetic analysis for intermediate γ-lactam **33**.

Attempted amide formation between **3** and **36** did not appreciably proceed in the presence of coupling reagents HBTU, HATU, PyBop or EDC. Instead, either a trace amount of the desired amide, decomposition of the amine, deprotection of the silyl group, or no reaction was observed under a variety of conditions. We attempted the amide bond formation via the mixed anhydride of acid **3**. Neither the isobutyl and ispropenyl nor 2,4,6-trichlorophenyl mixed anhydride provided any of the desired amide. Formation of the amide via the 2,3,4,5,6-pentafluorophenyl ester derivative of **3** also proved unsuccessful. Attempts to acylate amine **36** via an acid chloride formed by means of the Vilsmeier reagent and acid **3** yielded trace amounts of the desired product in certain cases, but often returned starting material and deprotected alcohol accompanied by decomposition of the acid chloride. After numerous attempts to couple amine **36** and acid **3** had failed, we revised our synthesis of aldehyde **34**.

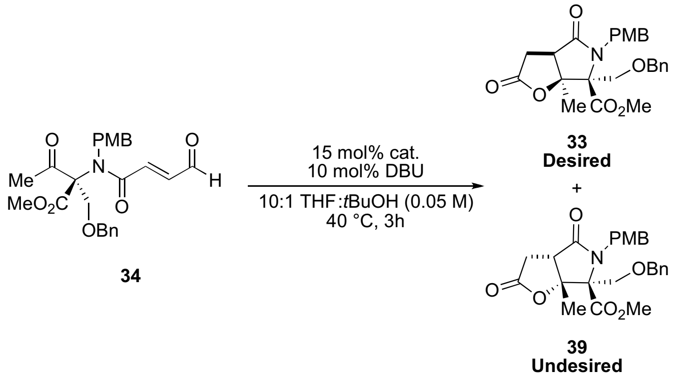
We instead accessed aldehyde **34** from amine **36** by first using a three-step sequence of N-acylation with sorbyl chloride, silyl ether cleavage under aqueous acidic conditions, and Dess–Martin oxidation[13] to afford ketone **37** in 60% overall yield. Next we performed a regioselective Sharpless dihydroxylation[14] at the γ,δ-position of **37** using a procedure similar to one reported by Zhang and O'Doherty[15] to access diol **38** as a single diastereomer in moderate yield. Finally diol cleavage was accomplished with sodium periodate in quantitative yield (Scheme 6).

Having successfully synthesized key intermediate **34**, we subjected the enal to our previously optimized conditions for cyclization of substrate **22**. When **34** was allowed to react with 15 mol% IMesCl and 10 mol% DBU in 10:1 THF/*t*-BuOH at 40 °C a complete conversion to the γ-lactam-γ-lactone products **33** and **39** was observed (Table 4, entry 1). Although the isolated yield was good (75%), the diastereomeric ratio was only 3:1 in favor of the undesired diastereomer. We therefore sought to bias the stereochemical outcome through the use of a chiral catalyst. We employed our *N*-mesityl aminoindanol derived chiral triazolium catalyst **29** (entry 2); the diastereomeric ratio decreased to 1.2:1 still in favor of the undesired diastereomer but with increased yield (84%). Interestingly, the use of *ent*-**29** provided nearly an identical outcome (entry 3). Triazolium salts, **12** and **31**, which had previously led to higher enantiomeric ratios with substrate **22** gave slightly higher diastereomeric ratios: 1.7:1 and 1.5:1, respectively, but again in favor of the undesired diastereomer (entries 4 and 5). Therefore, choice of the appropriate catalyst, *ent*-**29**, did indeed influence the strong substrate control over the diastereoslective homoenolate addition to the ketone whereby a 1:1.1 ratio of desired/undersired lactam is our best result (see entry 3). Our NHC-catalyzed intramolecular cyclization–lactonization of enal **34** provided lactams **33** and **39** in excellent yield and represents a formal synthesis of salinospoaramide A.



Scheme 6. Preparation of aldehyde **34** for NHC-catalyzed intramolecular cyclization–lactonization (DIPEA=*N*,*N*-diisopropylethylamine, Dess–Martin=1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, PMB=*p*-methoxybenzyl).

Table 4
NHC-catalyzed cyclization–lactonization of substrate **34**



Entry	Catalyst	Yield[a] (%)	dr (desired/undesired)
1	IMesCl	75	1:3
2	**29**	84	1:1.2
3	*ent*-**29**	88	1:1.1
4	**12**	93	1:1.7
5	**31**	77	1:1.5

All reactions listed proceeded with 100% conversion.
[a] Combined isolated yield of both diastereomers.

3. Conclusion

We have presented an NHC-catalyzed intramolecular cyclization–lactonization of enals to ketones tethered by an amide bond, producing densely functionalized γ-lactam-γ-lactone adducts. To demonstrate the utility of this method, we accomplished the formal synthesis of salinosporamide A, a potent 20S proteasome inhibitor, via intermediates reported by Corey and by Lam. The attraction of our synthesis is the use of an NHC-promoted intramolecular cyclization–lactonization strategy to construct the carbocyclic core of salinosporamide A in a single high-yielding step.

4. Experimental

4.1. General methods

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen. Dichloromethane was distilled over CaH_2. Diethyl ether, THF and *tert*-butanol were distilled from Na^0. Toluene and DMF were dried by passage over activated alumina under Ar atmosphere. All other reagents were used without further purification. Thin-layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid, cerium sulfate or potassium permanganate solutions. Silica gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF_{254} (Art 7747). Column chromatography was performed on E. Merck 13 Silica Gel 60 (230–400 mesh) using a forced flow of 0.1–0.5 bar. ^1H and ^{13}C NMR were measured on Bruker Avance II NMR at 500 and 125 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Amide rotamers, are marked by an asterisks (*). Infrared (IR) spectra were recorded on a JASCO FT:IR-430 spectrophotometer and are reported as wavenumbers (cm^{-1}).

4.2. General procedure for catalytic reactions

A vial was charged with the NHC precatalyst, the substrate, and purged with N_2(g). Next, the solvent was added followed by the base under an atmosphere of nitrogen. The vial was sealed and stirred at the designated temperature until the starting material was consumed as indicated by TLC analysis. Finally, the solvent was removed under reduced pressure and the crude reaction mixture purified by silica gel chromatography.

4.2.1. *(E)-Ethyl 4,4-diethoxybut-2-enoate*

To a 1.0 M solution of (*E*)-ethyl 4-oxobut-2-enoate (12.0 mL, 100 mmol, 1.00 equiv) in 200 proof EtOH cooled to 0 °C were added triethylorthoformate (12.8 mL, 120 mmol, 1.2 equiv) and concd aq HCl (0.100 mL, 1.16 mmol, 0.0116 equiv). The solution was stirred at 0 °C for 4 h, allowed to warm to rt, and stirred until the disappearance of the starting material by TLC analysis (ca. 4 h). The solution was concentrated under reduced pressure and dissolved in EtOAc (150 mL). This solution was washed with H_2O (150 mL), and the aqueous layer back-extracted with EtOAc (150 mL). The combined organic fractions were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a clear liquid (19.5 g, 88%). ^1H NMR ($CDCl_3$) δ 6.80 (dd, 1H, J=15.8, 4.2 Hz), 6.13 (dd, 1H, J=15.8, 1.3 Hz), 5.04 (dd, 1H, J=4.2, 1.3 Hz), 4.20 (q, 2H, J=7.1 Hz), 3.65 (dq, 2H, J=7.1, 2.3 Hz), 3.52 (dq, 2H, J=7.1, 2.4 Hz), 1.29 (t, 3H, J=7.1 Hz), 1.22 (t, 6H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 143.6, 124.2, 99.2, 61.4, 60.7, 15.3, 14.3; IR (thin film) ν 2981, 2927, 2878, 1722, 1446, 1373, 1304, 1269, 1181, 1058 cm^{-1}; $HRESI^+$/TOF-MS calcd for $C_{10}H_{18}O_4$ $[M]^+$ 202.1205, found 225.1106 $[M+Na]^+$.

4.2.2. *(E)-4,4-Diethoxybut-2-enoic acid (**3**)*

A 1 N aq solution of NaOH (20 mL, 20 mmol, 1.0 equiv) was added slowly to a chilled (0 °C) 1 M solution of (*E*)-ethyl 4,4-diethoxybut-2-enoate (4.0 g, 20 mmol, 1.0 equiv) in THF (20 mL). The solution was allowed to warm to rt and stirred until the consumption of starting material was observed by TLC (ca. 5 h). The solution was diluted with CH_2Cl_2 (100 mL) and the pH of the aqueous phase adjusted with 1 N aq HCl until pH ~ 2 was achieved. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (100 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a yellow liquid (3.5 g, quant). ^1H NMR ($CDCl_3$) δ 6.92 (dd, 1H, J=15.8, 4.0 Hz), 6.16 (dd, 1H. J=15.8, 1.4 Hz), 5.09 (dd, 1H, J=4.0, 1.3 Hz), 3.66 (dq, 2H, J=7.1, 2.4 Hz), 3.54 (dq, 2H, J=7.1, 2.4 Hz), 1.23 (t, 6H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 170.7, 150.5, 125.0, 103.3, 66.2, 15.1; IR (thin film) ν 3104, 2981, 2937, 2898, 1796, 1761, 1377, 1348, 1136, 1013, 929, 890, 817 cm^{-1}; $HRESI^-$/TOF-MS calcd for $C_8H_{14}O_4$ $[M]^+$ 174.0892, found 173.0803 $[M-H]^-$.

4.2.3. (E)-4,4-Diethoxy-N-(2-oxo-2-phenylethyl)but-2-enamide

N,*N*-Diisopropylethylamine (0.52 mL, 3.0 mmol, 3.0 equiv) was added to a solution of **3** (0.35 g, 2.0 mmol, 2.0 equiv) and HBTU (0.76 g, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL). After 10 min of stirring, 2-oxo-2-phenylethanaminium chloride (0.17 g, 1.0 mmol, 1.0 equiv) was added in a single portion and the solution stirred at rt for 20 h. The solution was diluted with CH_2Cl_2 (15 mL) and washed with satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with satd aq NH_4Cl (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography afforded the title compound as a white solid (0.195 g, 67%). ^{1}H NMR ($CDCl_3$) δ 8.00–7.98 (m, 2H), 7.63 (t, 1H, *J*=7.4 Hz), 7.51 (t, 1H, *J*=7.8 Hz), 6.78 (dd, 1H, *J*=15.5, 3.8 Hz), 6.70 (br s, 1H), 6.28 (dd, 1H, *J*=15.5, 1.4 Hz), 5.10 (dd, 1H, *J*=3.8, 1.4 Hz), 4.84 (d, 2H, *J*=4.3 Hz), 3.66 (dq, 2H, *J*=7.1, 2.4 Hz), 3.53 (dq, 2H, *J*=7.1, 2.4 Hz), 1.23 (t, 6H, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 194.1, 165.2, 140.5, 134.4, 129.1, 128.1, 125.9, 99.2, 61.3, 46.7, 15.4; IR (thin film) ν 3311, 2976, 2873, 1678, 1638, 1377, 1058, 1003, 979 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{16}H_{21}NO_4$ $[M]^+$ 291.1471, found 314.1356 $[M+Na]^+$.

4.2.4. (E)-4-Oxo-N-(2-oxo-2-phenylethyl)but-2-enamide (**1**)

A solution of (*E*)-4,4-diethoxy-*N*-(2-oxo-2-phenylethyl)but-2-enamide (0.10 g, 0.34 mmol, 1.0 equiv) in THF (4.0 mL) was treated with 2 N aq HCl (1.2 mL, 2.4 mmol, 7.0 equiv) at rt and stirred until the consumption of starting material was observed by TLC (ca. 5 min). The solution was diluted with H_2O (15 mL) and EtOAc (15 mL); the organic layer was separated, washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording the title compound as a light tan solid (0.074 g, quant). ^{1}H NMR ($CDCl_3$) δ 9.79 (d, 1H, *J*=7.4 Hz), 8.00 (dd, 2H, *J*=8.4, 1.2 Hz), 7.66 (dt, 1H, *J*=7.4, 1.2 Hz), 7.53 (t, 2H, *J*=7.5 Hz), 7.02 (dd, 1H, *J*=15.6, 7.4 Hz), 6.89 (d, 1H, *J*=15.6 Hz), 4.89 (d, 1H, *J*=4.3 Hz); ^{13}C NMR ($CDCl_3$) δ 193.5, 192.4, 163.4, 141.4, 138.3, 134.7, 129.2, 129.1, 128.2, 46.8; IR (thin film) ν 3316, 3060, 2922, 2848, 1695, 1675, 1670, 1540, 1358, 1230, 984 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{12}H_{11}NO_3$ $[M]^+$ 217.0739, found 240.0622 $[M+Na]^+$.

4.2.5. 1-(2-Oxo-2-phenylethyl)pyrrolidine-2,5-dione (**4**)

An oven dried vial was charged with IMesCl (0.0075 g, 0.022 mmol, 0.20 equiv) and **3** (0.023 g, 0.11 mmol, 1.0 equiv) and purged with N_2(g). To this mixture were added THF (1.0 mL) and DBU (3.3 μL, 0.022 mmol, 0.20 equiv), the vial sealed, and the reaction mixture stirred at 40 °C for 12 h. The solution was concentrated under reduced pressure and purified by PTLC (2:1 hexanes/acetone). ^{1}H NMR ($CDCl_3$) δ 7.97 (dd, 2H, *J*=8.4, 1.2 Hz), 7.63 (dt, 1H, *J*=7.4, 1.2 Hz), 7.52–7.49 (m, 2H), 4.95 (s, 2H), 2.87 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 190.3, 176.8, 134.3, 129.0, 128.3, 44.9, 28.5; HRESI$^+$/TOF-MS calcd for $C_{12}H_{11}NO_3$ $[M]^+$ 217.0739, found 240.0627 $[M+Na]^+$.

4.2.6. N-Benzyl-2-oxo-2-phenylethanaminium chloride (**5**)[16]

A 1.0 M solution of 2-bromo-1-phenylethanone (10.0 g, 50.0 mmol, 1.00 equiv) in Et_2O (50.0 mL) was added to a chilled (0 °C) 2.0 M solution of benzylamine (10.9 mL, 100 mmol, 2.00 equiv) in Et_2O over a 10 min period and stirred at 0 °C for 16 h. The precipitate was filtered and washed with Et_2O. The filtrate was cooled to 0 °C and concd HCl (4.0 mL) was slowly added. The resultant orange precipitate was filtered and washed with Et_2O. The precipitate was then sonicated in 60 mL of 1:1 Et_2O/EtOH (200 proof) until the solid appeared white. The precipitate was collected by filtration and washed with Et_2O affording 2.80 g (crop 1, 21.4%) of the title compound as a white crystalline solid. The filtrate was then concentrated and the resulting solid sonicated in a 1:1 Et_2O/EtOH (200 proof) solution until the solid appeared white. The precipitate was collected by filtration and washed with Et_2O affording an additional 3.70 g (crop 2, 28.2%) of the title compound as a white powder. ^{1}H NMR (DMSO-d_6) δ 9.45 (br s, 2H), 8.00–7.98 (m, 2H), 7.93–7.91 (m, 1H), 7.77–7.74 (m 1H), 7.63–7.60 (m, 2H), 7.56–7.54 (m, 2H), 7.48–7.44 (m, 2H), 4.82 (s, 2H), 4.21 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 192.2, 134.8, 133.7, 131.8, 130.3, 129.2, 128.8, 128.2, 128.1, 51.9, 50.2; IR (KBr) ν 2977, 2912, 2785, 2730, 2608, 2435, 1712, 1579, 1461, 1225, 742 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{15}H_{16}ClNO^+$ $[M]^+$ 226.1226, found 226.1223 $[M]^+$.

4.2.7. (E)-N-Benzyl-4-oxo-N-(2-oxo-2-phenylethyl)but-2-enamide (**6**)

To a solution of **3** (1.50 g, 8.61 mmol, 2.00 equiv) in CH_2Cl_2 (50.0 mL) were sequentially added **5** (1.12 g, 4.28 mmol, 1.00 equiv), EDC (1.65 g, 8.60 mmol, 2.00 equiv), 4-dimethylaminopyridine (0.525 g, 4.30 mmol, 1.00 equiv), and triethylamine (3.00 mL, 21.5 mmol, 5.02 equiv) and the resulting brown solution stirred for 24 h. The solution was diluted with CH_2Cl_2 (100 mL), washed with 1 N aq HCl (2×75 mL) followed by satd aq $NaHCO_3$ (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording a brown foam. The foam was dissolved in THF (13 mL) and treated with 6 N aq HCl (13 mL, 26 mmol, 6.0 equiv) for 1 h. After diluting the solution with CH_2Cl_2 (~70 mL) and H_2O (~50 mL) the organic phase was separated. The aqueous phase was further extracted with CH_2Cl_2 (2×50 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude aldehyde as a brown solid. Sonication of the crude solid in Et_2O/EtOAc precipitated the pure aldehyde as a tan solid and as a ~3:1 mixture of amide rotamers that was collected by vacuum filtration and washed with Et_2O (0.600 g, 46% over two steps). ^{1}H NMR ($CDCl_3$) δ 9.73 (d, 1H, *J*=7.5 Hz), 9.64* (d, 1H, *J*=5.2 Hz), 7.93 (d, 2H, *J*=7.5 Hz), 7.85* (d, 2H, *J*=7.5 Hz), 7.60–7.22 (m, 9H), 7.65–7.22* (m, 9H), 7.03 (dd, 1H, *J*=15.5, 7.5 Hz), 7.03* (dd, 1H, *J*=15.5, 7.5 Hz), 6.96 (d, 1H, *J*=5.5 Hz), 6.96* (d, 1H, *J*=5.5 Hz), 4.87 (s, 2H), 4.78 (s, 2H), 4.76* (s, 2H), 4.72* (s, 2H); ^{13}C NMR ($CDCl_3$) δ 193.4, 192.5, 165.8, 139.9, 139.7,139.4, 138.9, 135.7, 135.2, 134.7, 134.2, 129.5, 129.4, 129.1, 129.1, 128.9, 128.6, 128.2, 128.1, 126.9, 52.8, 52.2, 50.6; IR (thin film) ν 3065, 3035, 2932, 1697, 1647, 1451, 1358, 1230, 1117, 1077, 994 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{19}H_{17}NO_3$ $[M]^+$ 307.1208, found 308.1284 $[M+H]^+$.

4.2.8. N-Benzyl-2-oxo-N-(2-oxo-2-phenylethyl)-2-phenylethanaminium bromide (**14**)

Prepared by modification of a published procedure.[17] A 2.0 M solution of benzylamine (5.5 mL, 50 mmol, 1.0 equiv) in benzene (25 mL) was added to a 1.0 M solution of 2-bromo-1-phenylethanone (10 g, 50 mmol, 2.0 equiv) in benzene (50 mL). The resultant suspension was then diluted by the addition of an additional 30 mL benzene. The suspension was heated under reflux at 100 °C for 2 days. After allowing the reaction mixture to cool to rt, the precipitate was collected by vacuum filtration and washed with benzene (75 mL). The precipitate was suspended in MeOH (75 mL) and sonicated for 30 min. The precipitate was collected by vacuum filtration and washed with MeOH (25 mL). Residual solvent was removed under reduced pressure affording the title compound as a white powder (8.0 g, 75%). ^{1}H NMR (DMSO-d_6) δ 7.88 (d, 4H, *J*=7.3 Hz), 7.71 (t, 2H, *J*=7.4 Hz), 7.60–7.55 (m, 6H), 7.34–7.32 (m, 3H), 5.05 (br s, 4H), 4.51 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 191.4, 134.9, 132.0, 129.9, 129.2, 128.8, 128.4, 128.1, 60.2, 60.0; IR (KBr) ν 3011, 2977, 2922, 1692, 1604, 1451, 1254, 895 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{16}H_{22}NO_2^+$ $[M]^+$ 344.1645, found 344.1647 $[M]^+$.

4.2.9. Bis(2-oxo-2-phenylethyl)ammonium bromide (**15**)

A schlenk flask charged with 10% Pd/C (0.172 g, 0.162 mmol, 0.010 equiv of Pd) was evacuated and backfilled with H_2(g) 10 times. MeOH (75.0 mL) was added followed by **14** (6.88 g, 16.2 mmol, 1.0 equiv). H_2(g) was bubbled through the suspension until all of **14** had dissolved (ca. 8 h). The solution was filtered through Celite to remove the Pd/C, the Celite cake was washed with MeOH, and the filtrate concentrated under reduced pressure. The crude solid was recrystallized from MeOH to afford the title compound as a white solid (4.6 g, 85%). ^{1}H NMR (DMSO-d_6) δ 9.54 (br s, 2H), 8.00 (d, 4H, J=7.6 Hz), 7.76 (t, 2H, J=7.4 Hz), 7.62 (t, 4H, J=7.7 Hz), 4.84 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 192.2, 134.9, 133.6, 129.3, 128.3, 52.3; IR (KBr) ν 3001, 2912, 2814, 2716, 2588, 1687, 1599, 1554, 1368, 1259, 969 cm^{-1}; HRESI^{+}/TOF-MS calcd for $C_{15}H_{16}NO^{+}$ [M]$^{+}$ 226.1226, found 226.1232 [M]$^{+}$.

4.2.10. *(E)-4,4-diethoxy-N,N-bis(2-oxo-2-phenylethyl)-but-2-enamide (**16**)*

In a single portion, **15** (4.0 g, 12 mmol, 1.0 equiv) was added to a solution of **3** (4.2 g, 24 mmol, 2.0 equiv) in CH_2Cl_2 (120 mL). Next, EDC (4.6 g, 24 mmol, 2.0 equiv), 4-dimethylaminopyridine (1.5 g, 12 mmol, 1.0 equiv), and *N*,*N*′-diisopropylethylamine (10.5 mL, 60 mmol, 5.0 equiv) were sequentially added. The brown solution was stirred for 24 h at rt. After concentration of the solution under reduced pressure, the crude material was dissolved in EtOAc (250 mL) and sequentially washed with an aq 10% citric acid solution (2×125 mL), H_2O (100 mL), satd aq $NaHCO_3$ (2×125 mL), H_2O (1×100 mL), and brine (1×100 mL). The EtOAc solution was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (2:1 hexanes/EtOAc) afforded the title compound as a yellow foam (3.1 g, 63%). ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 4H), 7.63–7.55 (m, 2H), 7.50–7.43 (m, 4H), 6.74 (dd, 1H, J=15.3, 3.8 Hz), 6.38 (d, 1H, 15.3 Hz), 5.01 (s, 4H), 4.99 (d, 1H, J=3.8 Hz), 3.57–3.53 (m, 2H), 3.46–3.42 (m, 2H), 1.10 (t, 6H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 194.9, 194.0, 167.2, 142.1, 135.1, 134.6, 134.3, 133.9, 129.1, 128.9, 128.2, 128.0, 122.4, 99.2, 61.2, 54.9, 52.9, 15.2; IR (thin film) ν 3063, 2976, 2927, 1697, 1658, 1449, 1346, 1229, 1117, 1059, 1004, 756 cm^{-1}; HRESI^{+}/TOF-MS calcd for $C_{24}H_{27}NO_5$ [M]$^{+}$ 409.1889, found 432.1788 [M+Na]$^{+}$.

4.2.11. *(E)-4-Oxo-N,N-bis(2-oxo-2-phenylethyl)but-2-enamide (**13**)*

A 0.33 M solution of **16** (3.1 g, 7.6 mmol, 1.0 equiv) in THF (23 mL) was treated with 2 N aq HCl (23 mL, 46 mmol, 6.0 equiv) and stirred vigorously for 1 h at rt. The solution was diluted with EtOAc (125 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a yellow foam (2.5 g, quant). ^{1}H NMR ($CDCl_3$) δ 9.66 (d, 1H, J=7.1 Hz), 7.99–7.95 (m, 3H), 7.66–7.60 (m, 2H), 7.54–7.46 (m, 4H), 7.02 (d, 1H, J=15.7 Hz), 6.94 (dd, 1H, J=15.7, 7.1 Hz), 5.05 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 194.1, 193.3, 192.4, 166.0, 139.0, 136.1, 134.8, 134.7, 134.2, 134.1, 129.2, 129.0, 128.1, 128.1, 55.0, 53.1; IR (thin film) ν 3068, 2932, 2834, 2742, 1697, 1654, 1600, 1449, 1351, 1229, 1112, 917, 756 cm^{-1}; HRESI^{+}/TOF-MS calcd for $C_{20}H_{17}NO_4$ [M]$^{+}$ 335.1158, found 358.1031 [M+Na]$^{+}$.

4.2.12. *Benzyl 1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-ylcarbamate (**23**)*

To stirring solution of Cbz-AIB[18] (23.0 g, 96.9 mmol, 1.00 equiv) in CH_2Cl_2 (400 mL) were sequentially added *N*,*O*-dimethyl hydroxylamine hydrochloride (11.3 g, 116 mmol, 1.20 equiv), 4-dimethylaminopyridine (14.2 g, 116 mmol, 1.20 equiv), *N*,*N*′-diisopropylethylamine (20.0 mL, 116 mmol, 1.2 equiv), and *N*,*N*′-dicyclohexylcarbodiimide (11.3 g, 116 mmol, 1.20 equiv). The resultant suspension was stirred for 5 days. The precipitate was filtered and the filtrate diluted with CH_2Cl_2 (400 mL). This solution was sequentially washed with an aq 10% citric acid solution (2×400 mL), satd aq $NaHCO_3$ (2×400 mL), and H_2O (2×100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3:2 hexanes/EtOAc) afforded the title compound as white solid (18.0 g, 67%). ^{1}H NMR ($CDCl_3$) δ 7.35–7.29 (m, 5H), 5.77 (br s, 1H), 5.08 (s, 2H), 3.60 (s, 3H), 3.19 (s, 3H) 1.60 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 174.5, 154.7, 136.8, 128.6, 128.2, 66.4, 60.8, 57.3, 34.0, 24.2; IR (thin film) ν 3327, 3034, 2985, 2937, 1717, 1649, 1527, 1454, 1386, 1367, 1258, 1073, 995, 746, 698 cm^{-1}; HRESI^{+}/TOF-MS calcd for $C_{14}H_{20}N_2O_4$ [M]$^{+}$ 280.1432, found 303.1311 [M+Na]$^{+}$.

4.2.13. *Benzyl benzyl(1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (**24**)*

To a stirring solution of **23** (9.16 g, 32.7 mmol, 1.00 equiv) in DMF (165 mL) cooled to 0 °C was added NaH (60% mineral oil dispersion, 1.57 g, 39.2 mmol, 1.20 equiv). After effervescence had ceased (ca. 10–15 min), benzyl bromide (4.30 mL, 36.0 mmol, 1.10 equiv) was slowly added. The solution was allowed to warm to rt and stirred for 24 h. The solution was poured into a separatory funnel containing a solution of 1:1 satd aq NH_4Cl/brine (500 mL) and extracted with EtOAc (2×300 mL). The combined organic fractions were then washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (gradient, hexanes/EtOAc 2:1→4:3→1:1) afforded the title compound as a white solid (12.1 g, quant). ^{1}H NMR ($CDCl_3$) δ 7.30–7.24 (m, 10H), 5.22 (s, 3H), 4.68 (s, 2H), 3.38 (br s, 3H), 3.11 (br s, 3H), 1.43 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 175.2, 139.3, 136.5, 128.6, 128.4, 128.2, 127.5, 127.2, 67.5, 62.3, 60.0, 47.7, 33.8, 25.1; IR (thin film) ν 3033, 2990, 2939, 1697, 1665, 1401, 1356, 1228, 1095, 998, 699 cm^{-1}; HRESI^{+}/TOF-MS calcd for $C_{21}H_{26}N_2O_4$ [M]$^{+}$ 370.1893, found 393.1798 [M+Na]$^{+}$.

4.2.14. *Benzyl benzyl(2-methyl-3-oxobutan-2-yl)carbamate (**25**)*

Methyl magnesium bromide (3.0 M in Et_2O, 55.0 mL, 165 mmol, 5.00 equiv) was added slowly to a chilled solution (0 °C) of **24** (12.1 g, 32.7 mmol, 1.00 equiv) in Et_2O (165 mL). The suspension was allowed to warm to rt and stirred for 20 h. The suspension was cooled again to 0 °C and ice was carefully and slowly added over a 2 h period until the addition of more ice no longer caused gas evolution. The solution was decanted from the precipitate into a separatory funnel and diluted with EtOAc (300 mL) and H_2O (300 mL). The aqueous phase was removed; the organic phase was washed with brine (250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was sonicated in Et_2O and the title compound precipitated as a white solid that was collected by vacuum filtration (crop 1, 5.5 g, 59%). The filtrate was concentrated and then sonicated in a 3:2 solution of hexanes/Et_2O. Again the title compound precipitated as a white solid and was collected by vacuum filtration (crop 2, 2.0 g, 19%). ^{1}H NMR ($CDCl_3$) δ 7.30–7.24 (m, 10H), 5.16 (s, 2H), 4.64 (s, 2H), 2.05 (br s, 3H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 207.5, 156.6, 139.4, 136.2, 128.7, 128.6, 128.3, 127.3, 127.1, 67.9, 66.9, 47.5, 34.0, 23.6, 23.1; IR (thin film) ν 3063, 2985, 2941, 1722, 1693, 1458, 1405, 1351, 1253, 1220, 1088, 741 cm^{-1}; HRESI^{+}/TOF-MS calcd for $C_{20}H_{23}NO_3$ [M]$^{+}$ 325.1678, found 348.1579 [M+Na]$^{+}$.

4.2.15. *N-Benzyl-2-methyl-3-oxobutan-2-aminium chloride (**26**)*

A two-neck flask was purged with N_2(g) and then charged with 10% Pd/C (1.14 g, 1.08 mmol, 0.0500 equiv of Pd). The reaction vessel was evacuated and back-filled with H_2(g) three times before EtOH (200 proof, 100 mL) was added. Next, **25** (7.00 g, 21.5 mmol, 1.00 equiv) was added followed by concd HCl (3.70 mL, 43.0 mmol, 2.00 equiv). The heterogeneous solution was stirred at rt under an atmosphere of H_2(g) until the starting material was consumed as indicated by TLC analysis. Upon completion of the reaction, the solids were removed by filtration through a pad of Celite and the filter cake washed with MeOH. The filtrate was concentrated under reduced pressure to provide a crude white solid. The crude material was suspended in CH_2Cl_2 (200 mL), treated with satd aq $NaHCO_3$, and stirred at rt for 2 h. The biphasic mixture was transferred to a separatory funnel, the organic phase removed, and the aqueous phase extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure providing a crude oil. The oil was subjected to high vacuum to remove any 3-amino-3-methylbutan-2-one that resulted from over hydrogenation. The remaining crude material was dissolved in Et$_2$O (100 mL), cooled to 0 °C, treated with anhydrous HCl (4.0 M in dioxane, 5.40 mL, 21.6 mmol), and stirred for 30 min. The resultant precipitate was collected by vacuum filtration to afford the title compound as a white solid (4.31 g, 88%). ^{1}H NMR (CDCl$_3$) δ 9.89 (br s, 2H), 7.64 (d, 2H, J=7.0 Hz), 7.35–7.30 (m, 3H), 3.86 (t, 2H, J=5.9 Hz), 2.18 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 204.7, 131.4, 130.5, 129.5, 128.9, 67.4, 48.0, 24.5, 21.6; IR (thin film) ν 3424, 3034, 2917, 2855, 1720, 1547, 1453, 1133, 757, 702 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{12}H_{18}NO_3$ [M]$^+$ 192.1383, found 192.1390 [M]$^+$.

*4.2.16. (E)-N-Benzyl-4,4-diethoxy-N-(2-methyl-3-oxobutan-2-yl)but-2-enamide (**27**)*

Isobutyl chloroformate (0.52 mL, 4.0 mmol, 1.0 equiv) was dropwise added to a solution of **3** (0.70 g, 4.0 mmol, 1.0 equiv) and *N*-methylmorpholine (2.2 mL, 20 mmol, 5.0 equiv) in THF (20 mL) at −10 °C. The resultant suspension was stirred for 20 min at −10 °C before the addition of **26** (1.1 g, 4.8 mmol, 1.2 equiv). The reaction vessel was equipped with a water-jacketed condenser and heated at 50 °C for 20 h. After cooling to rt, the suspension was poured onto an aqueous 10% citric solution (50 mL) and extracted with EtOAc (75 mL). The organic extract was sequentially washed with aq 10% citric acid solution (50 mL), water (30 mL), satd aq NaHCO$_3$ (2×50 mL), water (30 mL), and brine (30 mL). The solution was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3:2 hexanes/EtOAc doped with 0.5%/vol NEt$_3$) provided the title compound (1.1 g, 78%). ^{1}H NMR (CDCl$_3$) δ 7.40–7.35 (m, 4H), 7.31–7.28 (t, 1H, J=6.8 Hz), 6.82 (dd, 1H, J=15.2, 4.0 Hz), 6.45 (d, 1H, J=15.2 Hz), 4.96 (d, 1H, J=4.0 Hz), 4.67 (s, 2H), 3.59–3.53 (m, 2H), 3.45–3.39 (m, 2H), 2.18 (s, 3H), 1.30 (s, 6H), 1.12 (t, 6H, J=7.0 Hz); ^{13}C NMR (CDCl$_3$) δ 206.1, 167.2, 142.9, 138.3, 129.1, 127.7, 126.3, 123.7, 99.5, 66.4, 61.5, 47.8, 24.4, 22.9, 15.2; IR (thin film) ν 3034, 2980, 2931, 2883, 1717, 1663, 1619, 1410, 1351, 1121, 1053, 737 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{20}H_{29}NO_4$ [M]$^+$ 347.2097, found 348.2163 [M+H]$^+$.

*4.2.17. (E)-N-Benzyl-N-(2-methyl-3-oxobutan-2-yl)-4-oxobut-2-enamide (**22**)*

A chilled (0 °C) solution of **27** (0.25 g, 0.72 mmol, 1.0 equiv) in THF (3.6 mL) was treated with 2 N aq HCl (2.1 mL, 4.3 mmol, 6.0 equiv). The solution was slowly allowed to warm to rt. Upon completion, as indicated by TLC analysis, the solution was diluted with EtOAc (25 mL), washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3:2 hexanes/EtOAc doped with 0.5%/vol NEt$_3$) provided the title compound as a white solid (0.13 g, 64%). ^{1}H NMR (CDCl$_3$) δ 9.62 (d, 1H, J=7.0 Hz), 7.46–7.33 (m, 5H), 7.06–6.97 (m, 2H), 4.74 (s, 2H), 2.23 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 206.0, 192.3, 165.8, 140.1, 137.4, 129.4, 128.2, 126.1, 66.8, 48.0, 24.7, 23.0; IR (thin film) ν 3034, 2985, 2931, 2849, 2736, 1712, 1693, 1644, 1419, 1351, 1254, 1117, 1029, 976 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{16}H_{19}NO_3$ [M]$^+$ 273.1365, found 274.1440 [M+H]$^+$.

*4.2.18. (3aR,6aR)-5-Benzyl-6,6,6a-trimethyltetrahydro-2H-furo[2,3-c]pyrrole-2,4(5H)-dione (**28**)*

Prepared according to the general procedure. The following procedure is representative. An oven-dried vial was charged with IMesCl (13.4 mg, 0.0393 mmol, 0.15 equiv) and **22** (72.0 mg, 0.263 mmol, 1.00 equiv). The vial was purged with N$_2$(g) and charged with 10:1 THF/*t*-BuOH (5.2 mL) and DBU (0.25 M solution in 10:1 THF/*t*-BuOH, 0.10 mL, 0.025 mmol, 0.10 equiv). The vial was capped and the reaction mixture stirred at 40 °C for 4.5 h. The solvent was removed under reduced pressure and the crude solid purified by flash column chromatography (gradient, hexanes/EtOAc/*i*-PrOH, 49:49:2→47.5:47.5:5) affording the title compound as a white foam (57.0 mg, 79%). ^{1}H NMR (CDCl$_3$) δ 7.31–7.28 (m, 2H), 7.26–7.21 (m, 3H), 4.52 (d, 1H, J=15.5 Hz), 4.41 (d, 1H, J=15.5 Hz), 3.08 (dd, 1H, J=18.0, 0.7 Hz), 3.03 (d, 1H, J=9.0 Hz), 2.89 (dd, 1H, J=18.0, 9.0 Hz), 1.45 (s, 3H), 1.26 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 174.0, 171.9, 137.9, 128.9, 127.6, 127.5, 90.2, 65.9, 46.5, 43.5, 31.7, 24.7, 20.2, 18.9; IR (thin film) ν 2976, 2937, 1780, 1693, 1410, 1268, 1229, 1200, 1122, 1083, 946 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{16}H_{19}NO_3$ [M]$^+$ 273.1365, found 296.1249 [M+Na]$^+$.

*4.2.19. (R)-Methyl 2-(benzyloxymethyl)-2-((2E,4E)-N-(4-methoxybenzyl)hexa-2,4-dienamido)-3-oxobutanoate (**37**)*

To a 0.50 M solution of **36** (0.357 g, 0.80 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (1.6 mL) cooled to 0 °C was added *N,N*′-diisopropylethylamine (0.21 mL, 1.2 mmol, 1.5 equiv). Sorbyl chloride[19] (0.125 g, 0.96 mmol, 1.2 equiv) was added dropwise and the solution stirred for 0.5 h at 0 °C before being allowed to warm to rt and stirred an additional 22 h. The solution was diluted with CH$_2$Cl$_2$ (20 mL), washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude material was dissolved in THF (4.0 mL) and treated with 6 N aq HCl (1.0 mL, 6.0 mmol, 7.5 equiv) at rt for 3 h. The solution was diluted with EtOAc (25 mL), washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude orange oil was dissolved in CH$_2$Cl$_2$ (8.0 mL), Dess–Martin periodinane (0.41 g, 0.96 mmol, 1.2 equiv) was added and the suspension stirred overnight. The solvent was removed under reduced pressure and the crude material taken up in EtOAc (30 mL). This was washed with a 1:1 solution of satd aq NaHCO$_3$/satd aq Na$_2$S$_2$O$_3$ (20 mL), wash$J$=8.6 Hz), 6.87–6.83 (m, 1H), 6.42 (d, J=15.0 Hz), 4.91 (d, 1H, J=18.4 Hz), 4.79 (d, 1H, J=18.3 Hz), 4.29 (d, 1H, J=11.9 Hz), 4.26 (d, 1H, J=11.9 Hz), 3.93 (br d, 1H, J=4.1 Hz), 3.81 (s, 3H), 3.78 (s, 3H), 3.74 (s, 2H), 3.62 (br s, 1H), 2.56 (d, 1H, J=5.0 Hz), 2.41 (s, 3H), 1.70 (br s, 1H), 1.14 (d, 3H, J=6.3 Hz); ^{13}C NMR (CDCl$_3$) δ 198.1, 169.2, 168.6, 158.9, 146.4, 136.8, 130.5, 128.5, 128.1, 127.7, 127.3, 121.6, 114.2, 77.5, 76.0, 73.9, 70.5, 70.2, 55.4, 53.0, 49.0, 28.2, 19.1; IR (thin film) ν 3420, 3029, 2932, 2878, 1737, 1712, 1658, 1615, 1517, 1409, 1361, 1244, 1092, 824 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{27}H_{33}NO_8$ [M]$^+$ 499.2206, found 500.2278 [M+H]$^+$.

*4.2.21. (R,E)-Methyl 2-(benzyloxymethyl)-2-(N-(4-methoxybenzyl)-4-oxobut-2-enamido)-3-oxobutanoate (**34**)*

A solution of **38** (0.043 g, 0.086 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (1.0 mL) was treated with satd aq NaHCO$_3$ (0.10 mL) and NaIO$_4$ at rt for 20 h. The heterogeneous mixture was filtered through a plug of Na$_2$SO$_4$ that was further washed with CH$_2$Cl$_2$ (15 mL). The filtrate was concentrated under reduced pressure to afford the title compound as a white foam (0.039 g, quant). ^{1}H NMR (CDCl$_3$) δ 9.56 (d, 1H, J=7.1 Hz), 7.38–7.33 (m, 2H), 7.31–7.26 (m, 3H), 7.13–7.11 (m, 2H), 7.01–6.92 (m, 4H), 4.97 (d, 1H, J=18.4 Hz), 4.81 (d, 1H, J=18.6 Hz), 4.32 (d, 1H, J=11.9 Hz), 4.28 (d, 1H, J=11.7 Hz), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 197.8, 192.4, 168.0, 167.5, 159.2, 140.2, 139.6, 136.5, 129.7, 128.6, 128.2, 127.8, 127.2, 114.5, 77.9, 74.0, 70.3, 55.5, 53.2, 49.2, 28.1; IR (thin film) ν 3006, 2953, 2922, 2834, 1742, 1694, 1651, 1513, 1412, 1357, 1248, 1110 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{25}H_{27}NO_7$ [M]$^+$ 453.1788, found 476.1665 [M+Na]$^+$.

*4.2.22. (3aR,6R,6aS)-Methyl 6-(benzyloxymethyl)-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydro-2H-furo[2,3-c]pyrrole-6-carboxylate (**33**) and (3aS,6R,6aR)-methyl 6-(benzyloxymethyl)-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydro-2H-furo[2,3-c]pyrrole-6-carboxylate (**39**)*

Prepared according to the general procedure. The following procedure is representative. An oven-dried vial containing **34** (12.4 mg, 0.027 mmol, 1.0 equiv) was charged with IMesCl (1.4 mg, 0.0040 mmol, 0.15 equiv). The vial was purged with N$_2$(g) and then charged with 10:1 THF/*t*-BuOH (0.55 mL) and DBU (0.50 μL, 0.0036 mmol, 0.10 equiv). The vial was capped and the reaction mixture stirred at 40 °C for 6 h. The solvent was removed under reduced pressure and the crude solid purified by flash column chromatography (hexanes/acetone, 3:1) to afford the mixture of diastereomers as a white film (9.3 mg, 75%).

*Data for **33***:[20] ^{1}H NMR (CDCl$_3$) δ 7.33–7.26 (m, 5H), 7.09 (d, 2H, *J*=6.8 Hz), 6.78 (d, 2H, *J*=8.6 Hz), 5.04 (d, 1H, *J*=15.2 Hz), 4.28 (d, 1H, *J*=15.2 Hz), 3.91 (d, 1H, *J*=11.5 Hz), 3.83–3.80 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.21 (d, 1H, *J*=10.4 Hz), 3.04 (d, 1H, *J*=9.3 Hz), 2.95 (d, 1H, *J*=18.3 Hz), 2.80 (dd, 1H, *J*=18.3, 9.6 Hz), 1.60 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 173.7, 173.1, 167.1, 159.2, 136.9, 130.2, 129.6, 128.6, 128.1, 127.5, 113.8, 88.6, 76.0, 73.0, 67.9, 55.4, 53.0, 47.7, 45.3, 30.9, 19.6; IR (thin film) ν 2956, 2922, 2853, 1790, 1761, 1702, 1614, 1512, 1454, 1400, 1249, 1181, 1131, 737 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{25}H_{27}NO_7$ [M]$^+$ 453.1788, found 476.1690 [M+H]$^+$.

*Data for **39***: ^{1}H NMR (CDCl$_3$) δ 7.36–7.29 (m, 3H), 7.20 (d, 2H, *J*=6.8 Hz), 7.08 (d, 2H, *J*=8.6 Hz), 6.78 (d, 2H, *J*=8.6 Hz), 4.67 (d, 1H, *J*=15.1 Hz), 4.37 (d, 1H, *J*=15.1 Hz), 4.30 (d, 1H, *J*=11.6 Hz), 4.25 (d, 1H, *J*=11.6 Hz), 3.89 (d, 1H, *J*=10.2 Hz), 3.78 (s, 3H), 3.71 (d, 1H, *J*=10.0 Hz), 3.63 (s, 3H), 3.04–2.99 (m, 2H), 2.84 (dd, 1H, *J*=18.4, 10.0 Hz), 1.47 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 173.6, 173.4, 169.4, 160.0, 137.3, 129.4, 129.2, 128.5, 128.0, 127.9, 86.8, 75.5, 73.8, 68.9, 55.4, 53.0, 47.2, 45.3, 31.1, 21.6; IR (thin film) ν 2951, 2927, 2853, 1790, 1746, 1702, 1610, 1512, 1439, 1249, 1127, 737 cm^{-1}; HRESI$^+$/TOF-MS calcd for $C_{25}H_{27}NO_7$ [M]$^+$ 453.1788, found 476.1691 [M+H]$^+$.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds associated with this article can be found in the online version at doi:10.1016/j.tet.2009.03.103.

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20. Although the ^{1}H NMR spectrum for **33** is an exact match to Lam's spectrum, there exists a discrepancy in our reported data at resonance 6.78 ppm due to a typo in Lam's report (δ 6.60 ppm); please see Ref. 8g and Supplementary data therein.