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Rapid Assembly of Complex Cyclopentanes Employing Chiral, α,β-Unsaturated Acylammonium Intermediates

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Abstract

Toward improving synthetic efficiency, organic chemists have turned to bioinspired organocascade or domino processes that generate multiple bonds and stereocenters in a single operation. However, despite the great importance of substituted cyclopentanes, given their prevalence in complex natural products and pharmaceutical agents, the rapid, enantioselective assembly of these carbocycles lags behind cyclohexanes. Herein, we describe a novel Michael-aldol-β-lactonization organocascade process for the synthesis of complex cyclopentanes utilizing chiral α,β-unsaturated acylammonium intermediates, readily generated by activation of commodity unsaturated acid chlorides with chiral isothiourea catalysts. This efficient methodology enables the construction of two C-C bonds, one C-O bond, two rings, and three contiguous stereogenic centers delivering complex cyclopentanes with high levels of relative and absolute stereocontrol. Our results suggest that unsaturated acyl ammonium intermediates have broad utility for the design of organocascade and multicomponent processes with the latter demonstrated by a Michael-Michael-aldol-β-lactonization.

Synthetic transformations that rapidly assemble complexity are actively being pursued given the importance of these processes for improvements in synthetic efficiency. In this regard, domino,[1,2] tandem,[3] and most recently organocascade[4,5] processes have emerged as some of the most useful strategies for quickly generating structural complexity.[6,7] Such methods for the construction of 6-membered carbocycles are numerous and include a range of classical methods with the Robinson annulation,[8] the cationic polyene olefin cyclization,[9] and the venerable Diels-Alder reaction[10] serving as benchmarks. By contrast the construction of 5-membered carbocycles falls short of such diverse and widely used methods.[11] While several elegant strategies exist for 5-membered carbocycle synthesis or annulation including the Pauson-Khand reaction,[12] trimethylenemethane [3+2] cycloaddition,[13] photochemical olefin-arene cycloaddition,[14] and the Nazarov cyclization,[15] most of these methods deliver cyclopentanes possessing no more than two stereogenic centers and most are not

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Author Contributions

G.L. initiated the studies of the α,β-unsaturated acyl ammonium intermediate from acid chlorides. D. R., G.L., and M.E.S. were involved in the design of experiments for exploration of the NCMAL. D.R. and K.N.V. conceived and developed the three-component NCMAL process. G.L., M.E.S., K.N.V., and R.L.M. performed the experiments. D.R., G.L., and M.E.S. composed the manuscript with input from all authors.

enantioselective. Organocatalytic methods for cyclopentane synthesis have begun to emerge, however many of these methods are quite limited in scope proceeding best with arene-substituted substrates.[16] To address the challenge of efficient enantioselective construction of stereochemically rich cyclopentanes, a common motif in bioactive natural products[17] and pharmaceuticals (Fig. 1a), we sought to design an organocascade process that could rapidly assemble these carbocycles from readily available materials.

Building on our interest in tertiary amine mediated nucleophilic catalysis,[18,19] we were attracted to the potential utility of chiral α,β-unsaturated acylammonium intermediates **3** given the presence of three disparate reactive sites that could be revealed sequentially to induce tandem bond-forming events (Fig. 2a). Within nucleophilic catalysis, chiral acylammonium intermediate **4**, bearing one electrophilic site, has proven exceedingly useful for kinetic resolution of alcohols.[20,21,22,23] The chiral ammonium enolate **5**,[24] bearing a nucleophilic site and a latent electrophilic site, is a highly versatile intermediate for a variety of transformations including aldol-β-lactonizations,[25,26,27] α-halogenation,[28] and hetero Diels-Alder reactions (Fig. 2b).[29] Another more recent member in this family of chiral intermediates is the ammonium dienolate **6** derived from γ-deprotonation of an α,β-unsaturated acylammonium intermediate.[30] We anticipated generation of the unsaturated acylammonium **3** through catalytic, asymmetric activation of acid chlorides by a chiral amine nucleophile (Fig. 2c). Following Michael addition by an appropriate nucleophile (Nuc^1), a chiral ammonium enolate **7** is revealed enabling α-substitution with an electrophile (E) to deliver the acylammonium **8**, and finally regeneration of the amine catalyst by acyl substitution with a second nucleophile (Nuc^2) would deliver the triply functionalized adduct **9** (Fig. 2c). If the reaction partners are tethered (dashed lines), a bicyclic adduct **9** would result. A seminal report by the Fu group in 2006 demonstrated the potential of unsaturated acylammonium catalysis employing an unsaturated acyl fluoride and a chiral 4-pyrrolidinopyridine derivative to deliver a net [3+2] cycloaddition with a silylated indene with moderate enantioselectivities.[31] The fluoride released during acyl substitution was required to increase the reactivity of the allylsilane nucleophile. This remained the only report employing this chiral intermediate until very recently when the Smith group reported the use of unsaturated, mixed anhydrides in combination with 1,3-dicarbonyl compounds to provide aryl-substituted enol lactones through an enantioselective, tandem Michael-enol-lactonization process.[32] It should be noted that in both of these previous reports, the full potential of the latent, triply-reactive, unsaturated acylammonium **3** was not realized through formation of three new bonds. Herein, we describe the development of a novel organocascade process involving a nucleophile-catalyzed, Michael-aldol-β-lactonization (NCMAL) sequence that rapidly generates stereochemically complex cyclopentanes from commodity unsaturated acid chlorides including both fused and bridged cyclopentyl systems (Fig. 1c). As a consequence of the terminating lactonization step, the NCMAL delivers β-lactone-fused cyclopentanes, a structural motif found in the natural products spongiolactone and vibralactone A (Fig. 1b) in addition to a growing family of activity-based probes for proteome profiling.[33] The NCMAL process was rendered enantioselective by use of chiral isothiourea nucleophilic catalysts[34,35] leading to the asymmetric synthesis of cyclopentanes with up to three contiguous stereocenters including quaternary carbons.

The envisioned catalytic cycle for the organocascade process would be initiated by an intermolecular Michael of a tethered, triply-reactive reagent **11**, such as anionic ketone **10**, to the α,β-unsaturated acyl ammonium intermediate **3**. The key, chiral intermediate **3** would be derived from simple substitution of a chiral amine catalyst (NR_3) **2** with an unsaturated acid chloride **1** (Fig. 2d). Generation of the versatile ammonium enolate **12** enables engagement of the pendant ketone in an intramolecular aldol-β-lactonization templated by a Li(I) cation to deliver a stereoselective aldol reaction leading to formation of cyclopentane **13**. Based on our previous studies, high *anti* diastereoselectivity was anticipated for β-substituted acid chlorides since this alleviates developing $A^{1,3}$-strain during the aldol-lactonization step (*cf.* **12**).[26] A final β-lactonization would deliver the fused β-lactone ring and regenerate the nucleophilic amine catalyst.

Results and Discussion

We first set out to identify a suitable Brønsted base to generate a reactive Michael donor from the latent anionic reagent, keto malonate **10a**. Our initial reaction conditions involved generation of the malonate anion with various Brønsted bases in the presence of a nucleophilic catalyst followed by slow addition of the acid chloride to the mixture. Use of the nucleophile alone or the strong Brønsted base, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) did not provide the desired bicyclic-β-lactone **14a** (Table 1, entries 1, 2). However, the synergistic action of DBU and a Lewis acid ($LiClO_4$, entry 3) afforded the desired product in 68% yield.[36] To ensure complete enolate formation, stronger lithium bases were studied and found to provide further improvement in yields (entries 4–6) up to 75% yield. Use of more weakly coordinating counterions such as sodium and potassium led to drastically lower yields (entries 7, 8), while magnesium afforded a comparable yield (entry 9). A brief screening of nucleophiles,[37] including 9-azajulolidine, revealed that 4-pyrrolidinopyridine (4-PPY) and LiHMDS was an optimal combination for the NCMAL process (entries 10, 11). As evidence for the requirement of the nucleophile, a control reaction without 4-PPY did not afford any β-lactone (entry 12).

With suitable conditions for the NCMAL process in hand, we probed variation of the Michael donors (Table 2a, entries 1–9). Successful Michael donors bore two electron-withdrawing groups, an important feature pointing to the requirement of a soft enolate for the Michael addition. These substrates were obtained in a single step by alkylation of the corresponding malonates with chloroacetone (Supplementary, S3–S11). As depicted in Table 2, a variety of keto diesters, diketones, and dinitriles (entries 1–5) participate in the NCMAL process to provide the desired cyclopentanes **14b–f** in 60–84% yields. When a β-keto ester or α-cyano esters were used as Michael donors (Table 2, entries 6–8), cyclopentanes **14g,h** were obtained in 65–73% yields with poor diastereoselectivity (dr 1–1.7:1) as expected, however this is inconsequential given that these diastereomers would ultimately converge to a single diastereomer following decarboxylation (*vide infra*). Introduction of an α-keto stereocenter, as in ketomalonate **10j**, also led to a mixture of diastereomers **14j** (dr 2:1) in 81% yield.

Variation of the Michael acceptors through the study of a diverse array of commercially available α,β-unsaturated acid chlorides was undertaken next. Under the optimized NCMAL

conditions, cyclopentanes were readily accessed bearing up to three contiguous stereocenters with excellent relative stereochemical control (Table 2b, entries 10–17). β-Substituted acid chlorides uniformly gave high diastereoselectivity, due to $A^{1,3}$-strain (*cf.* Fig. 2d).[38] The breadth of β-substituted acid chlorides proved to be fruitful allowing for installation of various functional groups leading to β-alkyl substituted cyclopentane **14k** (entry 10) and ester substituted cylopentane **14l** (entry 11). Aryl-substituted acid chlorides with varied electronic properties (entries 12–14) proceeded in 83–90% yields. Use of sorbic chloride (**1g**, entry 15) provided a 64% yield of cyclopentane **14p** but allowed for the installation of an alkene moiety on the cyclopentane providing a robust functional handle for subsequent manipulations and diversification. An α-substituted acid chloride **1h** (entry 16) was also reactive under standard conditions and afforded cyclopentane **14q** in 78% yield bearing two contiguous quaternary stereocenters, one of which is an all carbon quaternary center. Finally, a highly congested cyclopentane **14r** was accessible using α,β-dimethyl acryloyl chloride **1i** (entry 17) in 60% yield as a single diastereomer.

Toward applying this complexity-generating process to bioactive natural product synthesis, we next explored an enantioselective variant of the NCMAL process. Building on our previously described aldol-lactonization process,[26] the chiral isothiourea, homobenzotetramisole (HBTM) developed by Birman[39] was found to be the optimal catalyst to promote an enantioselective NCMAL (Table 3). Employing the aforementioned optimized conditions for the racemic NCMAL, HBTM uniformly delivered the cyclopentanes (+)-**14a,** (+)-**14c,** and (+)-**14d** in 59–74% yields and 93–96% ee (Table 3, entries 1–4). The bis-allyl malonate ester **10d** was of particular interest for enabling further functionalization or removal of an electron-withdrawing group from the cyclopentane adducts (+)-**14c** and (+)-**14d** through mild Pd(0)-catalyzed decarboxylative transformations (entry 3).[40] The absolute configuration of β-lactone (+)-**14a** was confirmed by X-ray analysis of a derivative following ring opening with *p*-bromobenzylamine (Supplementary, Fig. S3). The diketone substrate **10e** was also well tolerated in the asymmetric process, leading to diketo cyclopentanes (+)-**14e** in 61% yield and 95% ee (Table 3, entry 5). The practicality of the NCMAL process was demonstrated by a gram-scale reaction using dimethyl keto malonate **10a** as Michael donor delivered (+)-**14a** with comparable results (74% yield, 93% ee, Table 3, entry 2).

To probe whether the initial Michael addition could proceed in an enantioselective manner, we next studied β-substituted acid chlorides. Indeed, use of (*S*)-HBTM with acid chlorides **1b–c** and **1d,g** gave cyclopentanes (+)-**14k–l** and (+)-**14m,p** in 89–99% ee as single diastereomers in 62–95% yields (Table 3, entries 6–12) including those bearing ethyl ester and alkenyl substituents suitable for further functionalization. The relative and absolute stereochemistry of the alkenyl substituted cyclopentane (+)-**14p** was confirmed by X-ray analysis (Supplementary, Fig. S6). When β-substituted acid chlorides were studied, an important difference in reaction outcome was noted under standard conditions. Optimization studies revealed that extending the addition times of the acid chloride once again led to high conversions and enantioselectivities. A competitive, racemic background pathway with the NCMAL, in the case of β-substituted acid chlorides, is proposed for this difference (Supplementary, Table S1). Under these optimized conditions, use of (*R*)-HBTM as catalyst

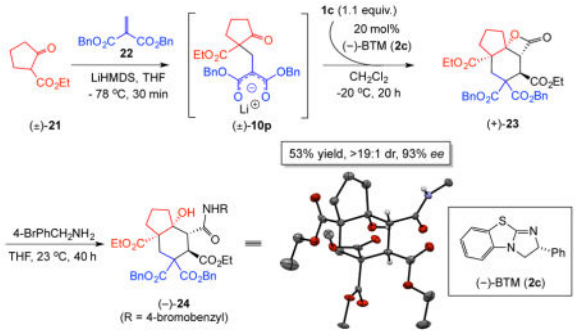
provided the enantiomeric β-lactones (−)-**14l** and (−)-**14p** in 90% yield, 89% ee and 60% yield, 99% ee, respectively (Table 3, entries 8 and 11). When applied to sorbic chloride (**1g**), the bis-allyl keto malonate **10c** provided cyclopentane (+)-**14s** in 55% yield and 94% ee as a single diastereomer. α-Methacrylolyl chloride (**1h**) was also a viable substrate delivering the sterically congested cyclopentane (+)-**14q** bearing two contiguous quaternary carbons, one being an all carbon quaternary center in 80% yield and 99% ee (entry 13).

To demonstrate the utility of the described organocascade process for ring annulation leading to more complex molecular architectures, a collection of polycyclic carbocycles with fused or bridged topology was targeted using monocyclic Michael donors. Cyclopentanone **10k** was readily combined with acryloyl chloride (**1a**) to give the tricyclic 5,5,4-bicyclic system **14t** as a single diastereomer in 91% yield (Fig. 3a). In contrast, cyclohexanone **10l** afforded the corresponding tricyclic products **14u** in 70% yield as a 1:1 mixture of diastereomers likely owing to the lower energy difference between *cis*- and *trans*-fused 5,6-bicyclic systems. Cyclohexanedione **10m** also participated as a Michael donor with acryloyl chloride (**1a**) to give the tricyclic cyclopentane **14v** possessing a bridged topology, albeit in 25% yield (Fig. 3b). The relative stereochemistry was confirmed by single crystal X-ray analysis (inset, Fig. 3b; Supplementary, Fig. S9) and the bridged cyclopentane in **14v** is reminiscent of one substructure of the gibberellin family of terpenoids (*cf.* Fig. 1a).[41] The tetralone-derived malonate **10n** also participated in the NCMAL, however the presumed intermediate β-lactone **15**, possessing a benzylic C-O bond, underwent facile decarboxylation to deliver the cyclopentene **16**. Following hydrogenation and Krapcho decarboxylation, the monoester **17** was obtained, demonstrating removal of an activating group in the Michael donor. Furthermore, the monoester **17** resembles a previously described steroidal intermediate[42] (*cf.* Fig. 1b). A milder method was also sought for removal of one of the activating groups required for competent, soft Michael donors. The Pd(0)-mediated decarboxylation of the allyl ester substituted cyclopentane **14i** was explored.[43] Mild conditions were identified that led to reductive decarboxylation of the mixture of diastereomeric cyclopentanes **14i** at 77 °C which importantly left the β-lactone intact and converged to a single diastereomer of the cyano-substituted cyclopentane **14x** bearing an additional stereocenter (Fig. 3d). The relative stereochemistry of **14x** was verified by X-ray analysis (inset, Fig. 3d; Supplementary Fig. S10). To the best of our knowledge, this is the first example of ester decarboxylation in the presence of a β-lactone (Fig. 3d).

Extension of the NCMAL from ketone substrates to the corresponding aldehyde malonates was expected to be challenging given the potential for side reactions of the reactive aldehyde under the basic conditions of the NCMAL. However, we were prompted to develop a strategy toward these types of bicyclic-β-lactones given the structure of vibralactone A (Fig. 1b). We envisioned that upon deprotonation of the malonate moiety of aldehyde **10o**, equilibrium would be established between the lithiated malonate anion **18** and the cyclopropyl lithium alkoxide **19** which could mask the reactivity of the aldehyde.[44] Indeed, metallation of aldehyde malonate **10o** and addition of acryloyl chloride (**1a**) in the presence of 20 mol% 4-PPY led to the desired cyclopentane **14y** in 60% yield.

We also demonstrated that *in situ* activated carboxylic acids could be utilized in the NCMAL greatly expanding the variety of accessible unsaturated acyl ammonium intermediates **3**. Commercially available cyclopentene acid **18a** was activated *in situ* with *p*-toluenesulfonyl chloride to the corresponding tosyl anhydride **18b** and without isolation, slow addition of this intermediate to the anion of keto malonate **10a** afforded the tricyclic 5,5,4-cyclopentyl system **14z** in 56% yield as a single diastereomer.

Towards combining the efficiency of the described organocascade with a multicomponent reaction,[45] we sought to perform an initial Michael reaction to obtain a competent Michael donor for the subsequent Michael-aldol-lactonization to rapidly achieve molecular complexity in a highly atom-economic manner. We envisioned that *in situ* generation of the ketomalonate anion **10p** through a Michael addition would initiate the cascade process and ultimately lead to a cyclohexyl fused-β-lactone **22**. Following extensive optimization, a three-component process was realized from β-ketoester **21**, fumaroyl chloride (**1c**), and dibenzyl 2-methylenemalonate (**22**) to provide the 6,5,4-tricyclic cyclohexane (+)-**23** in 53% yield and 93% ee generating four contiguous stereocenters, three new C-C bonds, one C-O bond, and two new rings in a highly stereoselective manner with (−)-BTM (**2c**) as nucleophilic promoter. The relative and absolute configuration was confirmed following ring opening of the β-lactone with *p*-bromobenzylamine to afford amide (−)-**23** (inset, Supplementary Fig. S11). This three-component reaction highlights the potential of incorporating α,β-unsaturated acylammonium intermediates **3** into the design of multicomponent, organocascade processes.



The complexity-generating, nucleophile-catalyzed, Michael-aldol-β-lactonization process described herein delivers high synthetic efficiency for complex cyclopentane synthesis by formation of three new bonds, up to three stereogenic centers, and two rings in a single operation from simple starting materials. Furthermore, the simple yet powerful asymmetric activation mode of commercially available, unsaturated acid chlorides utilized to its full potential for the first time by reaction at all three positions, provides a new paradigm for the design of additional organocascade processes. This tandem reaction was rendered highly enantioselective with the application of chiral isothiourea catalysts. Extensions to polycyclic carbon frameworks and multicomponent processes such as the Michael-Michael-aldol-lactonization demonstrate the potential of this concept for more sophisticated reaction design aimed at synthesis of natural products and pharmaceutical agents containing complex cyclopentanes. The β-lactones present in these systems are versatile platforms for further

transformations including dyotropic and Beckman rearrangements,[26] ring expansions,[46] enabling further elaboration of the cyclopentane products.[47] The combination of readily accessible catalysts ((*R*) and (*S*)-HBTM; soon available from Aldrich),[48] unsaturated acid chlorides (Sigma-Aldrich: 13 variously substituted, MatrixScientific: 37 β-aryl-substituted unsaturated, acid chlorides), and Michael donors (TCI, diethyl acetonylmalonate) in conjunction with *in situ* activated carboxylic acids enables an attractive and practical strategy for the expeditious synthesis of optically active cyclopentanes with correspondence to natural products and pharmaceutical agents. We anticipate that the described latent, triple reactivity of the unsaturated acyl ammonium intermediate will lead to additional, novel synthetic methods in the area of organocatalysis. Studies of additional transformations exploiting this underexplored activation mode of commodity unsaturated acid chlorides and synthetic applications of these methods are underway.

Methods

Gram-scale NCMAL leading to tricyclic-β-lactone (+)-14a

To an oven-dried, 250 mL round-bottomed flask equipped with a magnetic stir bar was added dimethyl 2-(2-oxopropyl) malonate (**10a**, 1.0 g, 5.32 mmol, 1.0 equiv.) along with THF (17 mL) and the mixture was cooled to −78 °C. With vigorous stirring, LiHMDS (5.32 mL of a 1.0 M solution in THF, 5.32 mmol, 1.0 equiv.) was added dropwise via gas tight syringe. After complete addition, the reaction was stirred for 10 min at −78 °C and then warmed to 0 °C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (60 mL), (*S*)-HBTM (283 mg, 1.06 mmol, dissolved in 7 mL CH_2Cl_2, 0.20 equiv.), and $EtN(^iPr)_2$ (0.93 mL, 5.32 mmol, 1.0 equiv.) were added sequentially via gas-tight syringe. The reaction was allowed to stir for an additional 10 min at 0 °C before acryloyl chloride (**1a**, 3.30 mL of a 1.612 M solution in CH_2Cl_2, 6.91 mmol, 1.30 equiv.) was added via microliter syringe dropwise over ~2 min. After complete addition, the ice bath was removed and the reaction was stirred for 6 h at ambient temperature (23 °C). The reaction was then cooled to 0 °C and silica gel (2 g) was added and stirred at 0 °C for 10 min. Then the ice/water bath was removed and the reaction stirred at ambient temperature (23 °C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 × 4 mL). The filtrate was then concentrated by rotary evaporation, and the crude mixture analyzed by ^{1}H NMR which indicated a >19:1 dr. Purification by an automated flash chromatography system (gradient of EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(+)-14a** (0.9497 g, 74%) as a colorless oil: Enantiomeric excess was determined by chiral GC analysis in comparison with authentic racemic material; t_{minor} = 251.6 min, t_{major} = 262.6 min; 93% *ee*. Spectral data matched that previously reported[26] and absolute stereochemistry was assigned following β-lactone ring opening with *p*-bromobenzylamine as described in the Supplementary.

Procedure for multicomponent Michael-Michael-aldol-β-lactonization delivering cyclohexane (+)-23

An oven-dried, 100-mL round-bottomed flask was charged with a solution of LiHMDS (1.80 mL of 1.0 M solution in THF, 1.80 mmol, 1.2 equiv,) in THF (2.5 mL) and cooled to

−78 °C. Following slow addition of a solution of cyclopentanone **21** (234 mg, 1.50 mmol, 1.0 equiv.) in THF (2.5 mL), the reaction mixture was warmed to −20 °C and stirred for 30 min. A solution of diester **21** (1.80 mL of 1.0 M solution in benzene, 1.80 mmol, 1.2 equiv) in THF (2.5 mL) was added dropwise. After 1 h at −20 °C, a solution of (−)-BTM (75.7 mg, 0.30 mmol, 20 mol%) and $EtN(^{i}Pr)_2$ (194 mg, 1.50 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added. Then a solution of acid chloride **1c** (366 mg, 2.25 mmol, 1.5 equiv.) in CH_2Cl_2 (5.0 mL) was added at −20 °C over 5 h by a syringe pump. The reaction temperature was maintained at −20 °C throughout the addition of **1b** and then the reaction was stirred at this temperature for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone (+)-**23** (457 mg, 53% yield) as a yellow, viscous liquid. Complete characterization data is provided in the Supplementary. The relative and absolute stereochemistry was confirmed by X-ray analysis (Supplementary Fig. S11) following β-lactone ring opening with *p*-bromobenzylamine.

Supplementary Material

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Acknowledgments

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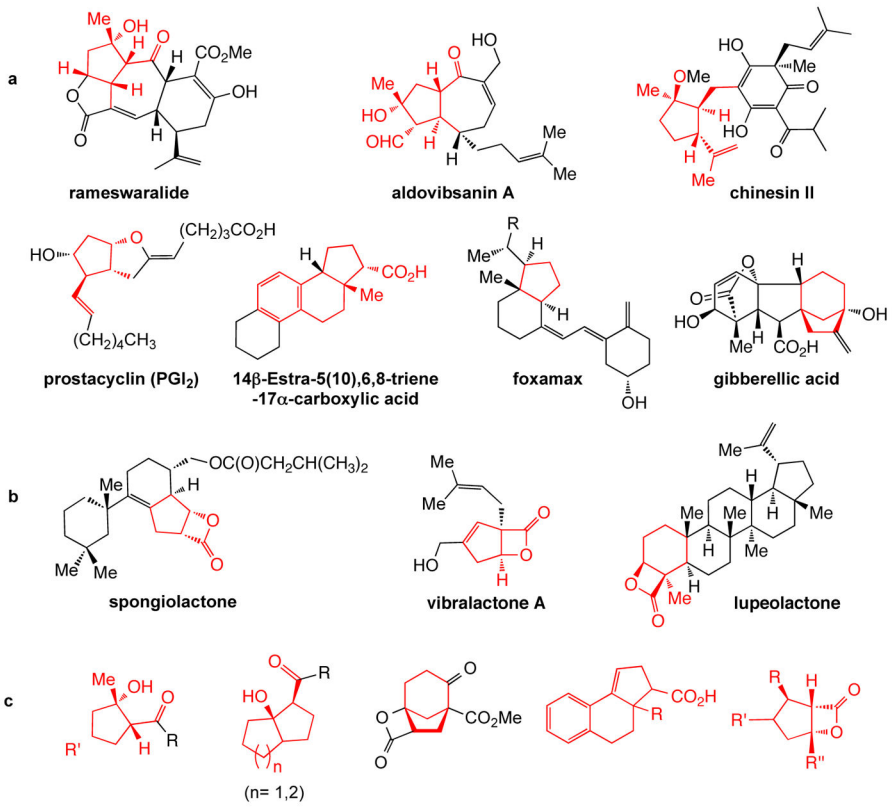


Figure 1. Natural products and pharmaceutical agents bearing complex cyclopentanes and accessible cyclopentyl systems employing the described NCMAL process

a, Bioactive natural products and drugs including polycyclics possessing highly substituted cyclopentane cores (red). **b**, Natural products possessing β-lactone-fused cyclopentanes (red). **c**, Several diverse cyclopentane scaffolds accessible by the described nucleophile-catalyzed, Michael-aldol-β-lactonization (NCMAL) process.

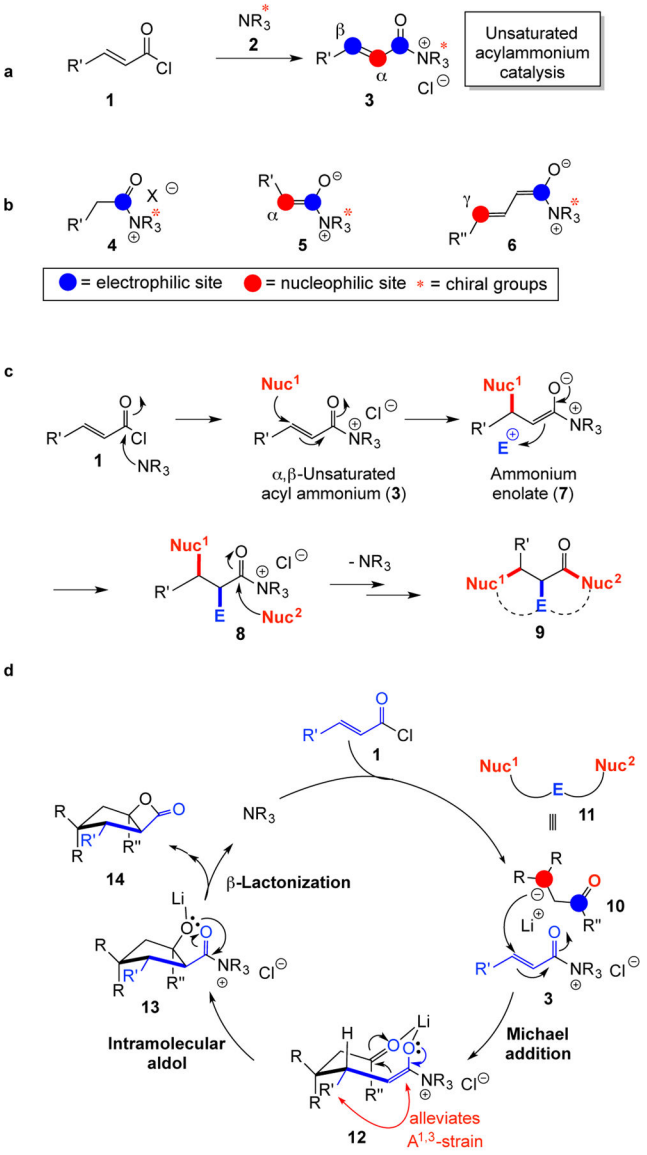


Figure 2. Generation and reactivity of the chiral unsaturated acylammonium 3 with contrast to related chiral intermediates 4–6 and a proposed catalytic cycle leading to bicyclic-β-lactones 14

a, Proposed synthesis of α,β-unsaturated acylammonium intermediate **3** from acid chlorides **1** and nucleophilic amines **2. b,** Related chiral intermediates include the acylammonium intermediate **4**, ammonium enolate **5**, and ammonium dienolate **6. c,** The latent, triple reactivity of the α,β-unsaturated acylammonium **3** first leads to an ammonium enolate **7** following Michael addition. The latter nucleophilic intermediate leads to α-substitution delivering acyl ammonium **8** and final acyl substitution leads to overall functionalizaton of three carbons of an α,β-unsaturated acid halide **1. d,** Proposed catalytic cycle employing a latent, triply-reactive species **10**, such as the keto anion **11**, possessing two nucleophilic and one electrophilic site, capable of reaction with unsaturated acyl ammonium **3** to form three bonds resulting in cyclopentanes **14** bearing a fused β-lactone through a Michael-aldol-lactonization organocascade process.

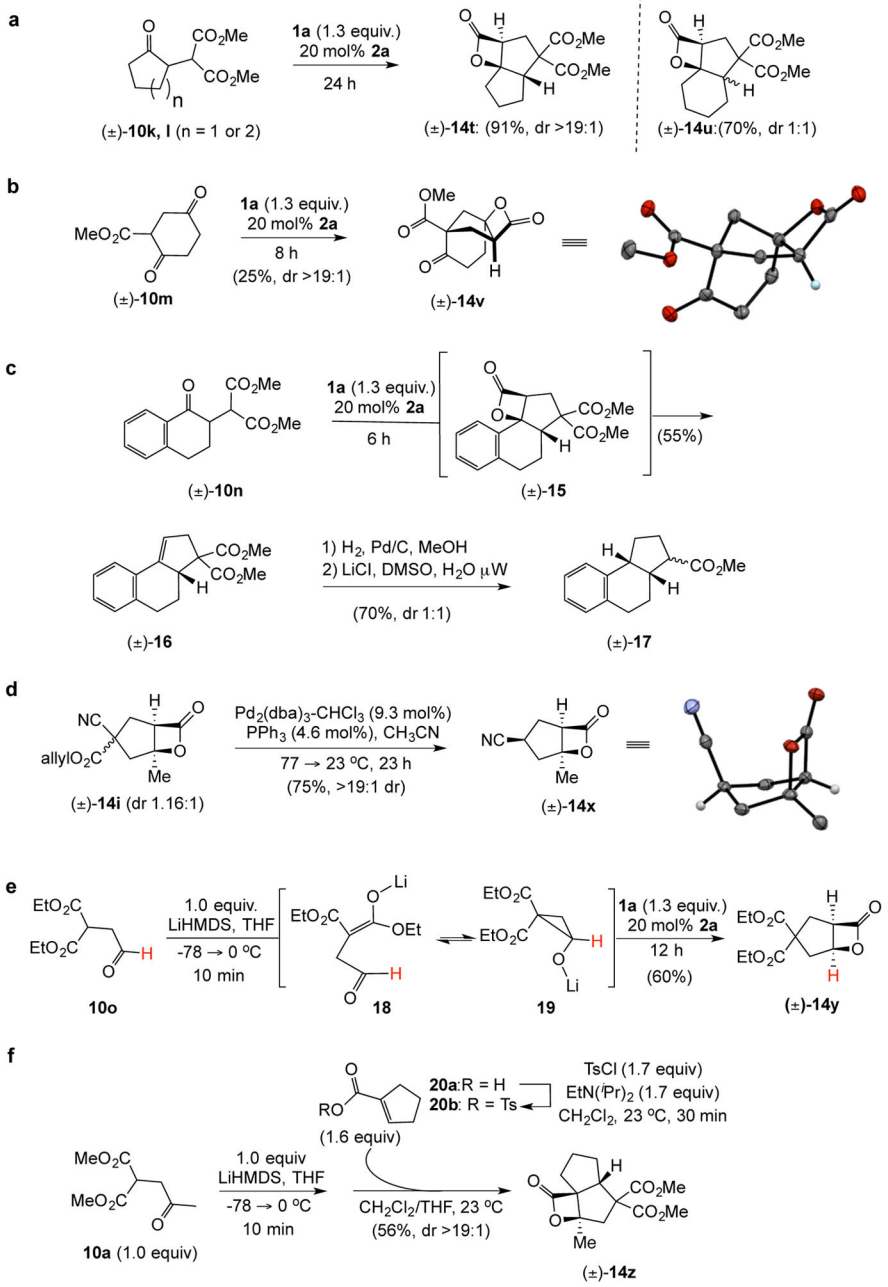


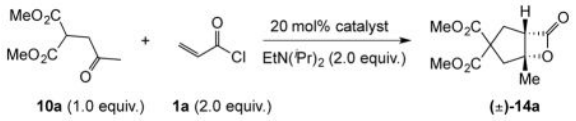
Figure 3. Rapid molecular complexity generation, structural modifications of cyclopentane products, and extensions of both accessible Michael donors and unsaturated acyl ammonium intermediates

[All NCMAL reactions were performed under standard reaction conditions shown in Table 2 unless noted otherwise.] **a,** Monocyclic Michael donors with acrylolyl chloride deliver tricyclic 5,5- and 5,6-fused cyclopentyl systems **14t** and **14u; b**, bridged tricylic cyclopentanes; and **c**, Truncated steroid intermediates through bis-decarboxylation; **d,** Mild Pd(0)-mediated reductive decarboxylations leads to cyano substituted cyclopentane **14x. e,** Application of aldehyde-containing Michael donors. **f**, *In situ* generation of tosyl anhydrides

delivers tricyclic 5,5,4-systems from starting carboxylic acids. Relative stereochemistry determined by X-ray analysis (Supplementary, Fig. S8).

Table 1

Optimization of the nucleophile-catalyzed, Michael-aldol-β-lactonization (NCMAL) process.



10a (1.0 equiv.) **1a** (2.0 equiv.) **(±)-14a**

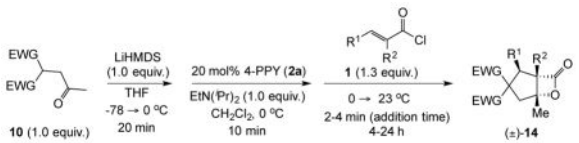
entry	base	catalyst	solvent	% yield*
1	--	DMAP	CH_2Cl_2	<5
2	DBU	DMAP	CH_2Cl_2	<5
3	$LiClO_4$+DBU	DMAP	CH_2Cl_2	68
4	LDA	DMAP	THF/CH_2Cl_2	73
5	^{n}BuLi	DMAP	THF/CH_2Cl_2	72
6	LiHMDS	DMAP	THF/CH_2Cl_2	75
7	NaHMDS	DMAP	THF/CH_2Cl_2	23
8	KHMDS	DMAP	THF/CH_2Cl_2	<5
9	^{i}PrMgCl	DMAP	THF/CH_2Cl_2	75
10	LiHMDS	4-PPY	THF/CH_2Cl_2	84
11	LiHMDS	9-AJ†	THF/CH_2Cl_2	77
12	LiHMDS	--	THF/CH_2Cl_2	<5

*Refers to isolated yields. <5% yield indicates that β-lactone was not detected by TLC, ^{1}H NMR (500 MHz), or FT-IR.

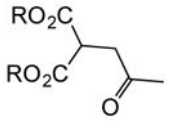
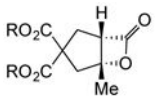
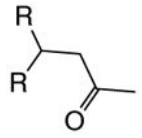
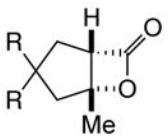
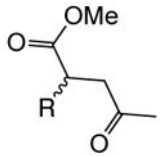
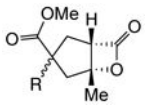
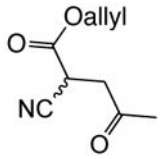
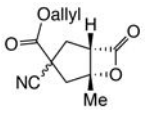
†9-azajulolidine (9-AJ).

Table 2

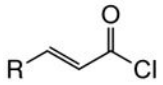
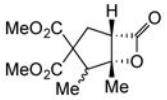
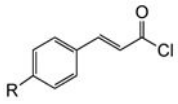
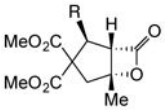
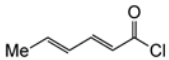
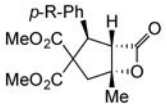
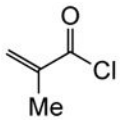
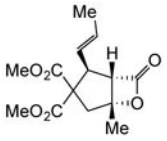
Scope of the nucleophile catalyzed, Michael-aldol-β-lactonization (NCMAL) organocascade process.

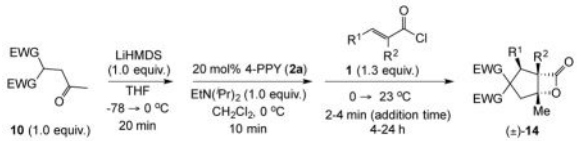


a Varying the Michael donor with acryloyl chloride 1a

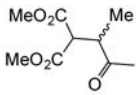
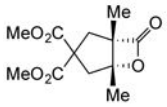
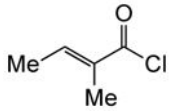
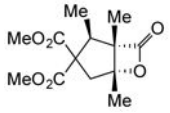
entry	starting material	bicyclic-β-lactone	% yield (dr)*
1			(±)-**14b:** R = tBu, 73
2			(±)-**14c**: R = allyl, 84
3	**10b-d**		(±)-**14d**: R = Bn, 63
4			(±)-**14e**: R = C(O)Me, 64
5			(±)-**14f**: R = CN, 60
	10e–f		
6			(±)-**14g**: R = C(O)Me 73 (1:1)
7			(±)-**14h**: R = CN 65 (1.7:1)
	(±)-**10g–h**		
8			60 (1.16:1)
	(±)-**10i**	(±)-**14i**	

b Varying the Michael acceptor with acetodimethyl malonate 10a*,†

entry	starting material	bicyclic-β-lactone	% yield (dr)*,†
10			(±)-**14k**: R = Me 94 (>19:1)‡
11			(±)-**14l**: R = CO_2Et 91 (>19:1)
12			(±)-**14m**: R = H, 90 (>19:1)‡
13			(±)-**14n**: R = NO_2, 83 (>19:1)
14			(±)-**14o**: R = OMe 87 (>19:1)
	1d–f	(±)-**14m–o**	
15			64 (>19:1)
	1g	(±)-**14p**	
16			78
	1h	(±)-**14q**	



a Varying the Michael donor with acryloyl chloride 1a **b Varying the Michael acceptor with acetodimethyl malonate 10a**[*,†]

entry	starting material	bicyclic-β-lactone	% yield (dr)[*]	entry	starting material	bicyclic-β-lactone	% yield (dr)[*,†]
9			84 (2:1)[†]	17			60 (>19:1)[‡]
	(±)-**10j**	(±)-**14j**			**1i**	(±)-**14r**	

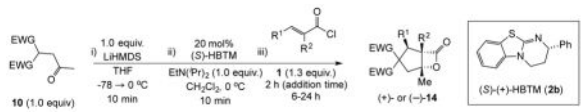
[*] All yields refer to isolated yields.

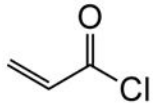
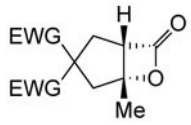
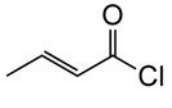
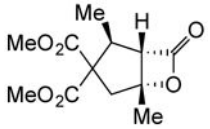
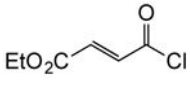
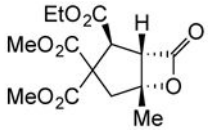
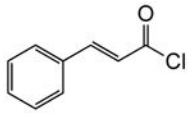
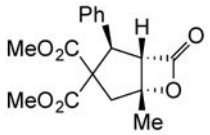
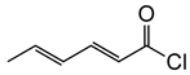
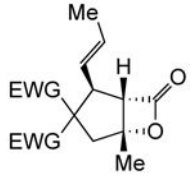
[†] Diasteromeric ratio determined by ^{1}H NMR.

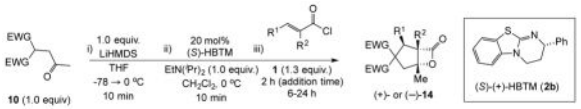
[‡] Relative stereochemistry verified by X-ray analysis. DMAP = 4-dimethyl amino pyridine,

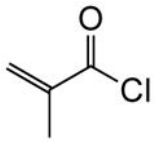
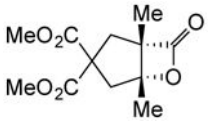
Table 3

Enantioselective nucleophile catalyzed, Michael–aldol-β-lactonization (NCMAL) organocascade.



entry	Michael donor (EWG)	acid chloride	bicyclic-β-lactone		% yield (dr)*	% ee
1†	**10a** (CO_2Me)	 **1a**		(+)-**14a**§	72	97
2†,‡	**10a**			(+)-**14a**	74	93
3†	**10c** (CO_2allyl)			(+)-**14c**	73	95
4†	**10d** (CO_2Bn)			(+)-**14d**	59	98
5†	**10e** (C(O)Me)			(+)-**14e**	61	95
6	**10a**	 **1b**		(+)-**14k**	80 (>19:1)	94
7†	**10a**	 **1c**		(+)-**14l**	95 (>19:1)	90
8†	**10a**			(−)-**14l**∫	90 (>19:1)	89
9	**10a**	 **1d**		(+)-**14m**	80 (>19:1)	99
10	**10a**	 **1g**		(+)-**14p**§	62 (>19:1)	99
11	**10a**			(−)-**14p**∫	60 (>19:1)	99
12	**10c**			(+)-**14s**	55 (>19:1)	94



entry	Michael donor (EWG)	acid chloride	bicyclic-β-lactone		% yield (dr)*	% ee
13	**10a**	 **1h**		(+)-**14q**	80 (>19:1)	99

*All yields refer to isolated yields, enantiomeric excess was determined by chiral GC or HPLC, diastereomeric ratios were determined by ^{1}H NMR (500 MHz), and addition of acid chloride was over a 2 h period. Reaction times varied from 6 to 24 h (see Supplementary for reaction details).

†Acid chlorides were added over 4 min.

‡Reaction was performed on gram scale.

§Absolute stereochemistry was confirmed by X-ray analysis of (+)-**14p** and a derivative of (+)-**14a** (Supplementary, Fig. S6 and Fig. S3, respectively). (*R*)-HBTM was employed as catalyst.