Multicomponent, Enantioselective Michael-Michael-Aldol-β-Lactonizations Delivering Complex β-Lactones

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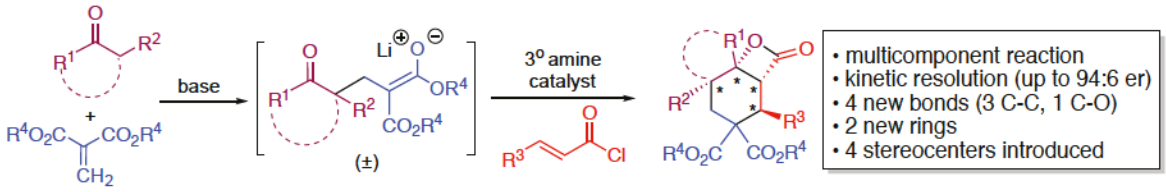


ABSTRACT: Optically active, tertiary amine Lewis bases react with unsaturated acid chlorides to deliver chiral, α,β-unsaturated acylammonium salts. These intermediates participate in a catalytic, enantioselective, three-component process delivering bi- and tricyclic β-lactones through a Michael-Michael-aldol-β-lactonization. In a single operation, the described multi-component, organocascade process forms complex bi- and tri-cyclic β-lactones by generating four new bonds, two rings and up to four contiguous stereocenters. In the racemic series, yields of 22-75% were achieved using 4-pyrrolidinopyridine as Lewis base. In the enantioselective series employing isothiourea catalysts, a kinetic resolution of the initially formed racemic, Michael adduct appears operative providing yields of 46% to quantitative (based on 50% max) with up to 93.5:6.5 er. Some evidence for a dynamic kinetic asymmetric transformation for tricyclic-β-lactone **1d** was obtained following optimization (yields up to 61%, 94:6 er) through a presumed reversible Michael.

Multicomponent reactions (MCRs) are transformations in which three or more substrates are combined to form a product in one pot without isolation of intermediates.[1] Compared to traditional sequential synthetic methods, MCRs can quickly deliver complex scaffolds through multiple bond forming events in a single operation while significantly reducing the time of preparation and purification in addition to labor and cost. These factors contribute to the

great utility of MCRs for chemists in a time when sustainable synthesis is sought.[2] The development of new MCRs increases the numbers of accessible targets with a common core structure through simple variation of each component making these processes popular for medicinal chemistry and drug discovery.[3] Despite these advantages, relatively few new multicomponent processes have emerged since their initial development nearly 100 years ago, and enantioselective MCRs are even more limited.[1,4] The field of organocatalysis has recently increased dramatically,[5] with new applications emerging constantly stemming from discovery of new reactivity and activation modes.[6] Not surprisingly, the joining of organocatalysis and MCRs is highly desirable.[7]

Ketones and aldehydes are ubiquitous components of MCRs mainly as a result of iminium/enamine catalysis, which is one of the most common activation modes employed for organocatalytic MCRs.[1,3-4,7] Seminal work in this area employing secondary amines includes the groups of Barbas,[8] MacMillan,[9] Jørgensen,[10] and Enders.[11] However, MCRs utilizing tertiary amine catalysis are rare.[1]

We previously described a method for the synthesis of bi- and tricyclic-β-lactones (*e.g.* β-lactone **1**) employing the intramolecular nucleophile (Lewis base)-catalyzed aldol β-lactonization (NCAL) process that relies on the intermediacy of chiral ammonium enolates (Figure 1a).[12] The groups of Smith,[13] Lupton,[14] Matsubara,[15] and Birman[16] and our group have described several organocascade processes that utilize chiral Lewis bases (nucleophilic catalysts) to generate chiral unsaturated acylammonium salts.[17] We utilized unsaturated acid chlorides as key intermediates for Michael-proton transfer-lactamizations,[18] nucleophile(Lewis base)-catalyzed, Michael-aldol-β-lactonizations (NCMAL),[19] Michael-enol lactonizations,[18,20] Diels-Alder-lactonizations[21] and Diels-Alder-lactamizations.[22] Despite the efficiency of generating three bonds in one operation using commodity acid chlorides, the NCMAL methodology requires the preparation of a malonate substrate bearing a pendant ketone or aldehyde. A potential solution we envisioned was the *in situ* generation of the required malonate substrate via a Michael addition between ketone **4** and an alkylidene malonate **5** that would also directly deliver the required malonate enolate (*e.g.* **6**) as a racemate. A subsequent enantioselective Michael-aldol-β-lactonization cascade involving a potential kinetic resolution of the derived racemic enolate (±)-**6** would deliver optically active bi- or tricyclic-β-lactones **1**. Herein, we detail complexity-generating, MCR organocascades that deliver bi- and tricyclic β-lactones **1** through formation of 3 C-C bonds, 1 C-O bond, 2 rings, and up to 4 stereocenters from commercially

available or readily available unsaturated acid chlorides **3**, ketones **4**, and alkylidene malonates **5**.

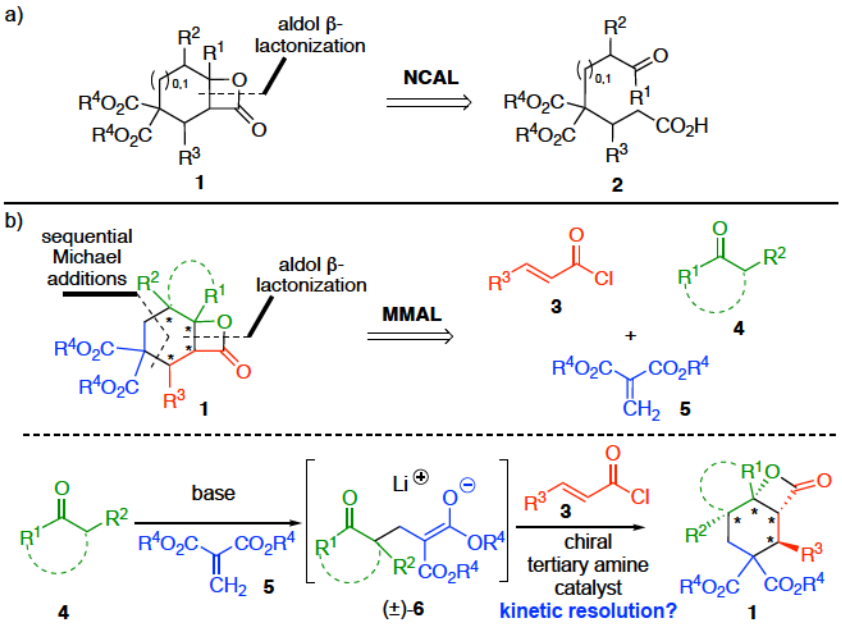


Figure 1. a) Previously described intramolecular nucleophile (Lewis base)-catalyzed aldol-β-lactonization (NCAL) process toward bicyclic-β-lactones. b) This work: a multi-component approach toward bicyclic-β-lactones *via* a Michael-Michael-aldol-β-lactonization involving a potential kinetic resolution.

The [4.2.0] bicyclic β-lactone motif is found in several bioactive natural products and is also a useful intermediate to access other structures.[23] Papyriogenin G,[24] isolated from a plant species used in traditional medicine to treat bacterial infections, inflammation and cancer, rubesanolides A/B,[25] and the unnamed, naturally occuring β-lactone **9** which exhibits thrombin inhibitory activity all bear the bicyclic β-lactone motif (Figure 2). In addition, the alkoxy acids **10** could potentially be obtained through hydrolysis and esterification of an appropriately substituted [4.2.0] bicyclic β-lactone.[26]

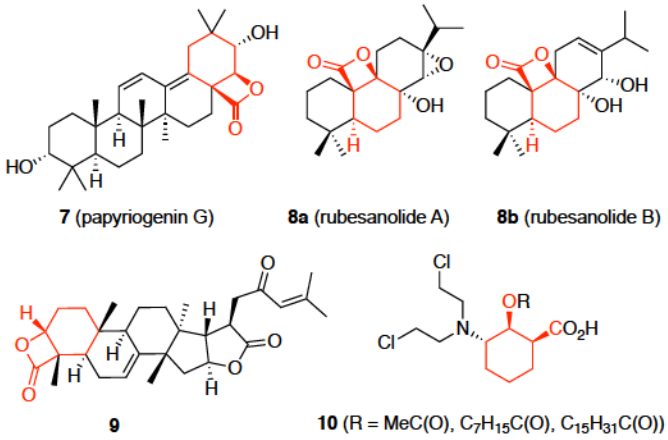
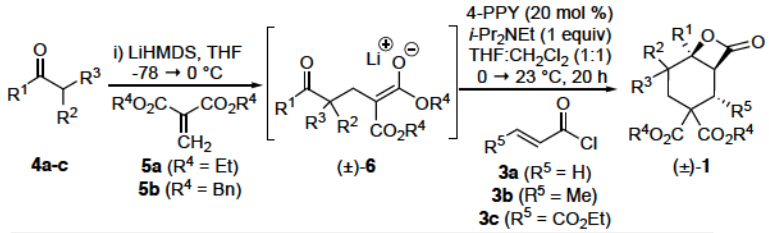
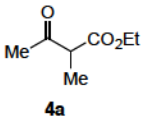
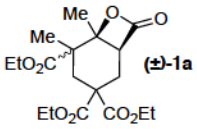
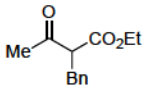
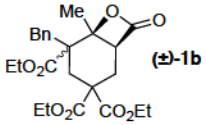
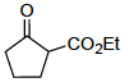
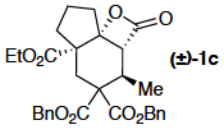
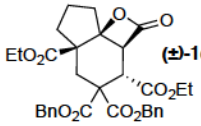
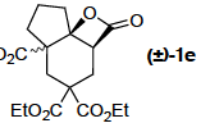


Figure 2. Natural products and bioactive molecules containing or potentially derived from [4.2.0] bicyclic-β-lactones (highlighted in red).

We began our studies by exploring various Michael donors and acid chlorides employing the achiral Lewis base, 4-pyrrolidinopyridine (4-PPY) for a MMAL delivering racemic product building on our single example reported previously.[19] Both cyclic and acyclic β-ketoesters along with diketones were studied in addition to simple ketones as Michael donors. The initial procedure involved deprotonation of the Michael donor **4** with LiHMDS, addition of alkylidene malonate **5**, 4-pyrrolidinopyridine (4-PPY), and Hünig's base, and finally slow addition of acid chloride **3** in a binary solvent, 1:4 THF/CH_2Cl_2. In our initial studies, we used acyclic Michael donor **4a**, methylene malonate **5a**, and acryloyl chloride (**3a**) which indeed gave the adduct **1a** in low yield. A brief optimization of a few reaction parameters revealed that 1:1 THF/CH_2Cl_2 gave the best yields providing the bicyclic β-lactone **1a** in 54% yield but as a 1:1 mixture of diastereomers (Table 1, entry 1). These conditions were then applied to other Michael donors and acid chlorides. Acyclic β-ketoester, α-benzyl β-ketoester **4b**, also gave the bicyclic β-lactone **1b** in 75% yield as a ~1:1 mixture of diastereomers. In contrast to the acyclic β-ketoesters, cyclic β-ketoester **4c** gave adduct **1c** as a single diastereomer (>19:1, crude ^{1}H NMR) employing crotonoyl chloride albeit in <10% yield, however use of racemic HBTM led to some improvement in conversion (22%, Table 1, entry 3). Use of the more reactive Michael acceptor, ethyl fumaroyl chloride (**3c**), led to an improved yield of adduct **1d** (32%, Table 1, entry 4). Employing highly reactive acryloyl chloride led to further improvement delivering tricyclic β-lactone **1e** in 58% yield with useful diastereoselectivity (9:1) (Table 1, entry 5). Other Michael donors (*e.g.* cyclohexanone, 2,4-pentanedione, 2-methyl-1,3-cyclohexanedione, 3,4-dihydronaphthalen-2(1*H*)-one, 3,3,5,5-tetramethylcyclohexan-1-one), Michael acceptors (bis-sulfonyl, bis-cyano, and β-phenyl and β,β-dimethyl alkylidene malonates), and acid chlorides (β-*i*-propyl, β-phenyl, α,β-dimethyl and β-propenyl acryloyl chloride) were investigated, however only trace amounts of β-lactones were detected by IR analysis of crude reaction mixtures (β-lactone C=O stretch: ~1820 cm^{-1}; see SI for further details).

Table 1. Screening Michael donors **4** in the MMAL organocascade delivering racemic β-lactone **1**



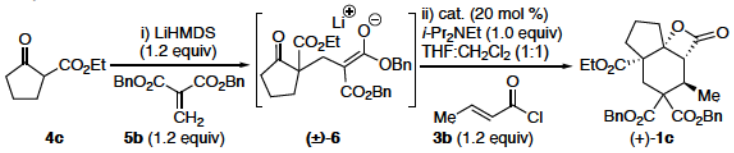
entry	Michael donors **4**	acid chloride **3**	β-lactones **1**	yield,[a] dr
1	 **4a**	**3a**	 **(±)-1a**	54%, 1:1
2	 **4b**	**3a**	 **(±)-1b**	75%, 1:1
3	 **4c**	**3b**	 **(±)-1c**	22%[b], > 19:1
4	**4c**	**3c**	 **(±)-1d**	32%, > 19:1
5	**4c**	**3a**	 **(±)-1e**	58% 9:1 (syn:anti)

[a]Yields refer to isolated yields. [b]Racemic HBTM ((±)-**14**, 20 mol %) was used as Lewis base and the reaction was performed at -20 °C.

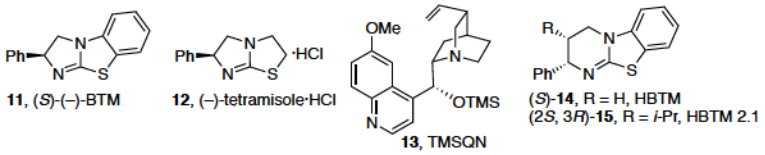
We next optimized the enantioselective variant of this organocascade employing the cyclic β-ketoester **4c** and crotonoyl chloride (**3b**) since racemic HBTM ((±)-**14**) had previously delivered β-lactone **1c** in low yield (Table 1, entry 3). The UV active dibenzyl methylenemalonate **5b** was employed to facilitate optical purity determination by chiral HPLC. It is important to note that without equilibration of the initial Michael reaction, if a kinetic resolution is operative, the maximum yield would be 50%. However, if equilibration is possible, a dynamic kinetic asymmetric transformation (DYKAT) is possible. Given the typically high enantioselectivity observed with isothiourea catalysts, we anticipated a matched/mismatched pairing between the enantiomeric malonate anions **6** and the chiral unsaturated acylammonium salt would lead to a kinetic resolution. Several chiral Lewis bases were screened including the commercially available isothiourea Lewis bases benzotetramisole (BTM, **11**) and tetramisole (**12**). These gave

the desired adduct **1c** in moderate enantiomeric ratios (Table 2, entries 1-3). The silylated cinchona alkaloid, TMSQN (**13**), led to an improved enantioselectivity (93:7 er) albeit in only 18% yield (Table 2, entry 4). Improvements in both yields and enantioselectivity were observed when the isothiourea catalysts HBTM (**14**) and HBTM 2.1 (**15**) were employed (Table 2, entries 5-9). In particular, use of HBTM 2.1 (**15**), a readily prepared derivative of Birman's HBTM Lewis base developed by Smith,[27] delivered tricyclic β-lactone **1c** in 43% yield and 93.5:6.5 er (Table 2, entry 7). Neither increasing the amount of acid chloride **3b** (Table 2, entry 8) nor reversing the stoichiometry of the reagents (Table 2, entry 9) led to any further improvement in yields or enantioselectivity of the desired β-lactone **1c**. The maximum yield obtained (<50%) provides indirect evidence that a kinetic resolution of the initially formed Michael adduct (±)-**6** is indeed in operation.

Table 2. Optimization of the enantioselective MMAL with cyclopentyl Michael donor **4c** and crotonoyl chloride (**3b**)



entry	cat. (20 mol %)	temp	yield (%)	dr	er
1	(*S*)-**11**	-20 °C	18	>19:1	88:12
2	(*R*)-**11**	-20 °C	22	>19:1	20:80
3	**12**	-20 °C	12	>19:1	79:21
4	**13**	-20 °C	18	>19:1	93:7
5	**14**	-20 °C	31	>19:1	76.5:13.5
6	**14**	0 → 23 °C	13	>19:1	93.5:6.5
7	**15**	0 °C	43	>19:1	6.5:93.5
8[a]	**15**	0 °C	41	>19:1	6:94
9[b]	**15**	0 °C	40	>19:1	13.5:86.5

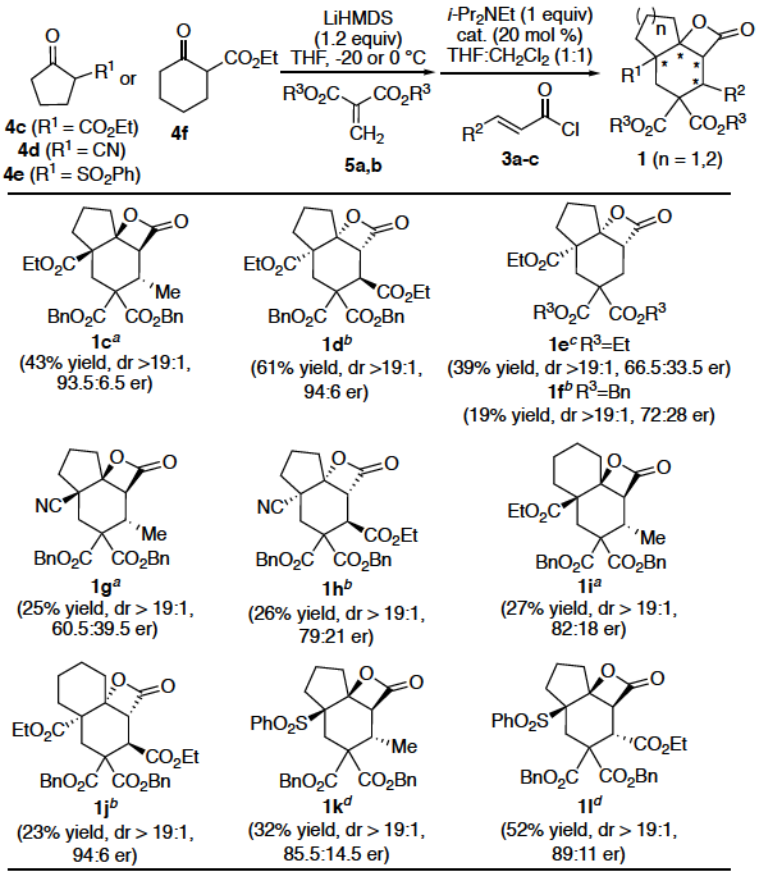


[a]Performed with 2.0 equiv of **3b.** [b]Performed with 2.0 equiv of **4c**, 2.1 equiv of **5b** and 1.0 equiv of **3b.**

We next sought to expand the scope of the enantioselective MMAL by studying various electron withdrawing groups on both cyclopentyl and cyclohexyl Michael donors **4** and the use of various acid chlorides **3** (Table 3). Ethyl fumaroyl chloride (**3c**, $R^2 = CO_2Et$) and Michael donor **4c** with BTM (**11**) gave a 61% yield of the tricylic adduct **1d** with a 94:6 enantiomeric ratio. This yield suggests that a DYKAT is in operation to some extent and may reflect the greater stability of the highly conjugated unsaturated acylammonium salt derived from **3c**. When acryloyl chlo-

ride (**3a**) was used with both the ethyl (**5a**) and benzyl (**5b**) alkylidene malonates, the enantiomeric ratio dropped dramatically to 66.5:33.5 and 72:28 for er adducts **1e** and **1f**, respectively. Reduced enantioselectivity was also observed when an α-cyanocyclopentanone (**4d**) was employed as Michael donor leading to adducts **1g** and **1h**, respectively. We propose that the inability to form a bidentate chelate with the Li cation in the intermediate β-cyano enolates of these Michael donors may lead to less ordered transition states and therefore reduced enantiomeric ratios. The importance of Li^+ as a counter ion, versus Na^+ for example, enabling chelation with the Michael donor (enolate) and Michael acceptor (carbonyl of unsaturated acyl ammonium salt) (*cf.* Li chelate, Fig. 4, inset) was also observed in our previously described Michael-proton transfer-enol-lactamization and lactonization.[18] α-Carboethoxy cyclohexanone Michael donor **4f** with α-methylacryloyl chloride (**3b**) and ethyl fumaroyl chloride (**3c**) also delivered the anticipated adducts **1i** and **1j**, respectively, albeit in reduced yields. α-Phenylsulfonyl Michael donor **4e** was also a suitable substrate in this reaction producing **1k** and **1l** in moderate yield and enantioselectivity. Generally, BTM (**19**) was the superior catalyst for ethyl fumaroyl chloride (**3c**) while HBTM 2.1 was better suited for the less reactive crotonoyl chloride (**3b**). As previously reported, the relative and absolute stereochemistry of β-lactone **1d** was confirmed by X-ray crystallography of a derived amide.[19] The relative and absolute stereochemistry of other tricylic β-lactones was assigned by analogy to **1d** along with coupling constant analysis (see SI for details). As expected, the enantiomeric series of cycloadducts was obtained when (2*S*, 3*R*)-HBTM 2.1 (**15**) was utilized as Lewis base versus (*S*)-BTM (**11**) and this was confirmed by comparative chiral HPLC.

Table 3. Substrate scope of the enantioselective MMAL organocascade

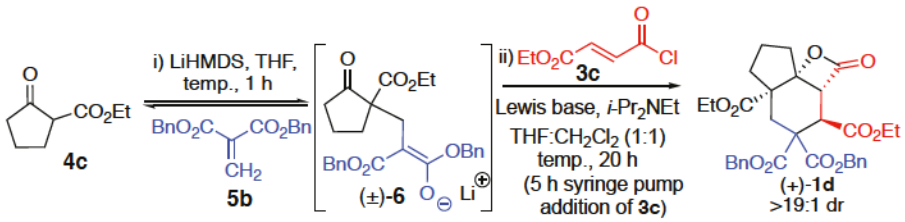


[a]Performed with 20 mol% **15** at 0 ºC, 0.1 M conc. [b]Performed with 20 mol % **11** at -20 ºC, 0.1 M. [c]Performed with 20 mol % (S)-**11** at 0 → 23 ºC, 0.1 M. [d]Performed with 20 mol% **15** at 0 → 23 ºC, 0.05 M.

While the reaction yields of most of these multicomponent organocascade processes remained below 50% as expected for a kinetic resolution, due to a presumed slower mismatched catalyst/substrate enantiomeric pair, a few substrates under varying conditions did provide >50% yield with enantiomeric ratios indicative of a potential dynamic kinetic asymmetric transformation (DYKAT) (*e.g.* adduct **1d**).[28] The potential for a DYKAT was investigated further by screening several reaction parameters (catalysts and catalyst loadings, reaction times, temperatures) to determine if conditions could be identified to increase yields through a retro-Michael addition enabling racemization of the initial Michael adduct (±)-**6**. Selected optimization reactions are provided in Table 4. Initial reaction conditions involved deprotonation of ketoester **4c** at -78 °C then addition of Brønsted and Lewis bases at the same temperarute followed by warming to 0 °C and syringe pump addition of acid chloride **3c** at that temperature. Increased reaction times did not improve the yield, however increased catalyst loading to 40 mol% and warming to ambient temperature led to the first yields above 50% (entry 3). Use of

thermodynamic base conditions (Hunig's base/LiCl) with a 72 h reaction time did provide the desired product but in lower yields (45%) and lower er (entry 4). Lowering the reaction temperature for the 2nd stage of the process did lead to an increase in yield (53%) with a shorter reaction time being optimal (20 vs 72 h, entry 6). Increasing the equivalents of the highly reactive Michael acceptor **5b** did not improve conversion (entries 7,8). Running the entire sequence at -20 ºC and a shorter initial deprotonation (30 min) led to the best conversion (61%, entry 9) with good enantioselectivity (94:6 er) and comparable results were obtained with the enantiomeric benzotetramisole catalyst (entry 10). Addition of LiHMDS to the mixture of ketoester **4c** and malonate **5b** did not alter the results (entry 11). Other isothiourea catalysts including HBTM (**14**) and HBTM 2.1(**15**) did not lead to further improvements (entries 12,13). In summary, the maximum yield achieved for this presumed DYKAT was ~60% and likely reflects the high reactivity of the alkylidene malonate **5b** regenerated upon a retro-Michael reaction.

Table 4. Optimization studies of a potential DYKAT involving the MMAL organocascade leading to tricyclic-β-lactone (+)-**1d**

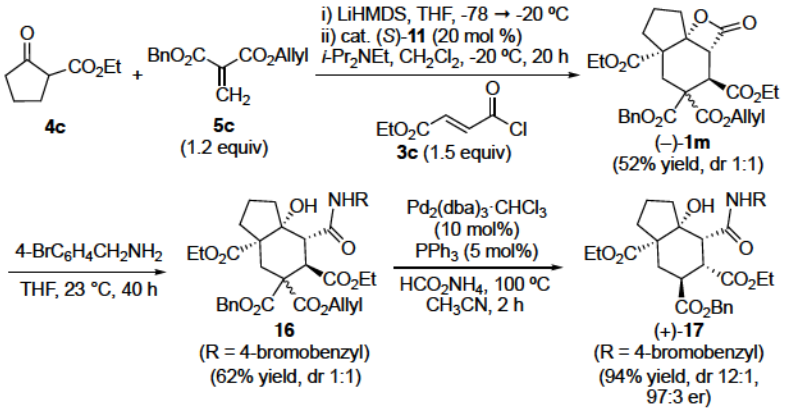


Entry	Lewis base (mol %)	Conditions	% Yield, er
1	(*S*)-(–)-**11** (20)	-78→0→23 ºC, 5.5 h	43, 94.5:5.5
2	"	-78 → 0 → 23 ºC, 20 h	47, 94.5:5.5
3	" (40)	"	56, 97.5:2.5
4	" (20)[a]	23 ºC, 72 h	45, 90:10
5	" (20)	-78 → -30 ºC, 72 h	30, 91.5:8.5
6	"	-78 → -20 ºC, 20 h	53, 96.5:3.5
7	" (20)[b]	-78 → -20 ºC, 20 h	46, 96:4
8	" (20)[c]	"	47, 95.5:4.5
9	" (20)[d]	-20 ºC, 20 h	61, 94:6
10	(*R*)-(+)-**11** (20)[d]	"	57, 90:10[f]
11	(*S*)-(–)-**11** (20)[e]	-20 ºC, 20 h	53, 90:10
12	(2*S*,3*R*)-**15** (20)[d]	0 ºC, 20 h	28, 82:18[f]
13	(*S*)-**14** (20 mol%)	-78 → 0 → 23 ºC, 20 h	39, 82:18

All the reactions were performed with 1.0 equiv of **4c**, 1.2 equiv of **5b** and 1.5 equiv of **3c** unless indicated otherwise: [a] Thermodynamic base conditions, *i*-Pr_2NEt (3 equiv) and LiCl (1 equiv), rather than LiHMDS were used to generate the malonate anion. [b] 2 equiv of compound **5b** was used. [c] 4.0 equiv of **5b** was used. [d] 30 min reaction time for step 1. [e] **4c** and **5b** were combined prior to addition of LiHMDS. [f] Enantiomeric adduct (–)-**1d** was obtained.

We recognized the potential to introduce an additional stereocenter *via* a Tsuji-Trost Pd(0)-mediated deallylative decarboxylation with an appropriate malonate bearing a single allylester.[29] Tricyclic β-lactone (–)-**1m** was prepared from the allyl, benzyl methylenemalonate **5c** and acid chloride **3c** in 52% yield (Scheme 1). The β-lactone was determined to not be compatible with temperatures required for the deallylative decarboxylation, thus it was opened with benzylamine to deliver amide **16**. Subjecting this amide to standard deallylative decarboxylation conditions gave benzyl ester (+)-**17** in 94% yield (12:1 dr). Under these decarboxylation conditions, the α-ethyl ester epimerized to the *anti*-1,2-diester in high diastereomeric purity. The enantiomeric purity of the major diastereomer was determined at this point and found to be 97:3 er (12:1 dr).

Scheme 1. Synthesis of bicyclic amide (+)-**17** bearing five stereogenic centers



The relative and absolute stereochemistry of amide **17** was determined through NMR experiments including DEPT 135, ^1H-^{13}C HSQC, ^1H-^1H COSY, ^1H-^{13}C HMBC which were used to assign the H1, H2, and H3 protons. A NOESY experiment showed key correlations between H1 and H2, and H2 and H3. Coupling constants ($J_{H1\text{-}H2}$ = 3.9 Hz, $J_{H2\text{-}H3}$ = 5.4 Hz) were then used to assign relative stereochemistry of **17** (Fig. 3). The absolute stereochemistry of **17** was assigned by analogy to β-lactone **1d** (secured through X-ray analysis of a derived amide[19]) employing the same Lewis base promoter, (–)-BTM (**11**).

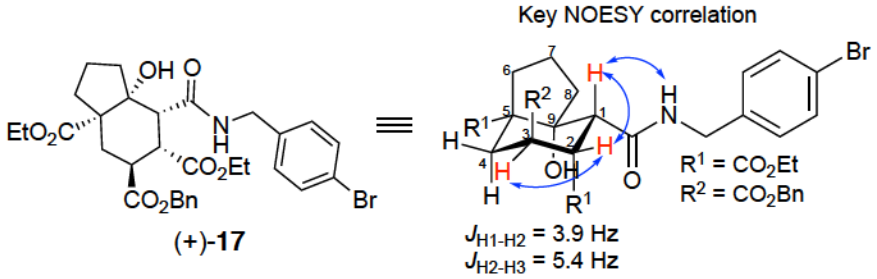
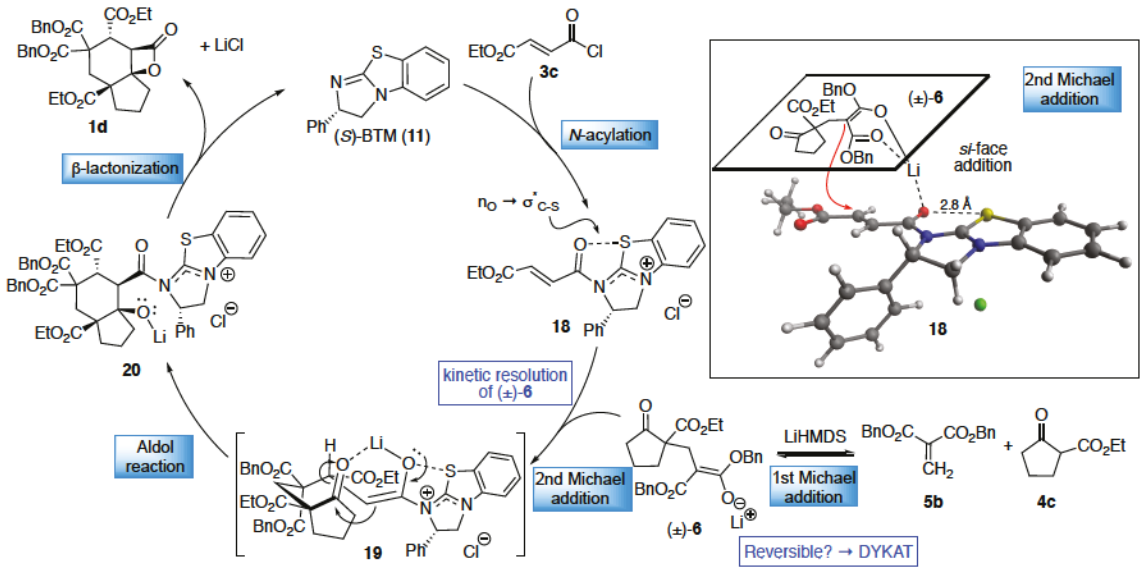


Figure 3. Key coupling assignments and NOESY correlations enabling assignment of the relative stereochemistry of amide (+)-**17**.

A proposed catalytic cycle for the MMAL process is shown in Figure 4. During the MMAL organocascade, an *in situ* generated, racemic Michael adduct (±)-**6** from β-ketoester **4c** and alkylidene malonate **5b** is formed initially. Based on a previously described DFT-calculated model of the unsaturated acylammonium salt **18** derived from BTM (**11**),[21b] this intermediate adopts an extended *s-cis* conformation of the unsaturated amide and alleviates non-bonded interactions enforced by a proposed $n_o \rightarrow \sigma^*_{C\text{-}S}$ interaction.[21b,13a,13c,30] The chiral α,β-unsaturated acylammonium salt **18** then undergoes a stereochemical-setting Michael reaction with one enantiomer of enolate (±)-**6** leading to a kinetic resolution and proceeding from the least hindered face, opposite the phenyl group of the catalyst via a possible Li-chelate as depicted (inset, Figure 4). The intermediate ammonium enolate **19**, bearing a pendant ketone, can adopt a chair-like transition state arrangement enforced by a presumed Li-bidentate chelate enabling the aldol β-lactonization to form β-lactone **1d** via aldolate **20**. We previously reported that the diastereoselectivity of the initial aldol reaction is substrate-controlled due to $A^{1,3}$-strain[12b] and the ring strain associated with formation of an alternative *trans*-fused bicyclic system further enforces this diastereoselectivity in the aldol step followed by a rapid β-lactonization to give β-lactone **1d**. Again, yields that only reach 61% provide some evidence for a DYKAT but the described MMAL is primarily a simple kinetic resolution.

Figure 4. Proposed catalytic cycle for the MMAL reaction and DFT-derived conformational model of the HBTM-derived acylammonium salt (inset)



[a]The energy-minimized conformation of unsaturated acylammonium **18** was computed using SMD(DCM)-M06-2X/6-31G(d) (see refs. 18,21b) Inset shows the second, stereochemical-setting Michael addition and the proposed Li+ chelate between the acylammonium and the Michael donor.

In conclusion, chiral α,β-unsaturated acylammonium salts are useful intermediates for a catalytic, enantioselective, three-component organocascade providing access to tricyclic β-lactones through a Michael-Michael-aldol-β-lactonization. In a single operation, this organocascade forms four bonds, two rings and up to four contiguous stereocenters with serviceable enantio- and diastereoselectivity. While some evidence for a DYKAT process was found for this organocascade proceeding through a presumed Michael-retro-Michael process, maximum yields were 53-61% (94:6 → 97.5:2.5 er). By exploiting this multicomponent process, complex, stereochemically rich bi- and tricyclic structural motifs can be accessed in a single step that also importantly bear a β-lactone, useful for further functionalizations[17a,31] and as tools for activity-based proteomics.[32]

EXPERIMENTAL SECTION

General information

All non-aqueous reactions were performed under a nitrogen or argon atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) were dried by passing through activated molecular sieves or alumina (solvent purification system). Diisopropylethylamine (*i*-Pr_2NEt) was distilled from potassium hydroxide prior to use. Other solvents and reagents were used as received from commercially available sources. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received. ^1H

NMR spectra were measured at 600, 500, 400 and 300 MHz and referenced relative to residual chloroform (7.26 ppm) and was reported in parts per million. Coupling constants (*J*) were reported in Hertz (Hz), with multiplicity reported following usual convention: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; m, multiplet; bs, broad singlet; app, apparent. ^{13}C NMR spectra were measured at 150, 125, 100, and 75 MHz and referenced relative to residual chloroform (77.2 ppm) and was reported in parts per million (ppm). Flash column chromatography was performed with 60Å Silica Gel (230-400 mesh) as stationary phase using a gradient solvent system or on an automated flash chromatography system (EtOAc/hexanes as eluent unless indicated otherwise). High resolution mass spectra (ESI) were obtained through Texas A&M University Laboratory for Biological Mass Spectrometry and Baylor University Mass Spectrometry Center. Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F254 (Silicycle, 250 m thickness). Visualization of developed plates was performed by fluorescence quenching unless indicated otherwise. *Fourier* Transform Infrared (FTIR) spectra were recorded as thin films on NaCl plates. Optical rotations were recorded on a polarimeter at 589 nm employing a 25 mm cell. High Performance Liquid Chromatography (HPLC) was performed on a chromatographic system using various chiral columns (25 cm) as noted. X-ray analysis was performed in the X-ray Diffraction Laboratory at Texas A&M University.

O-TMS quinine[33] (TMSQN) was synthesized according to literature procedures. Benzotetramisole, (+)-BTM and (–)-BTM were purchased from TCI chemicals**.** Acid chlorides **3a-c** were purchased from Sigma-Aldrich and used as received.

Safety/Hazards

PhSeBr is highly toxic and careful handling should be exercised. Specifically, besides standard personal protection equipment (lab coat, goggles, and gloves), minimum inhalation exposure was ensured by handling of this reaction in a well-ventilated hood or in closed vial when being weighed. The residual amount of PhSeBr, left in vials or syringes, was quenched with sat. solution of $Na_2S_2O_3$ followed by appropriate disposal of the solution and containing vessels.

Diethyl 2-methylenemalonate (5a). The alkylidene malonate was prepared by a modified literature procedure.[34] Into an oven-dried, 500-mL round-bottomed flask equipped with a stir bar was placed NaH (60% suspension in mineral oil, 1.50 g, 37.5 mmol, 1.5 equiv) and THF (90 mL) under N_2. The slurry was cooled to 0 °C and diethyl 2-methylmalonate (purchased from Sigma-Aldrich and used as received) (4.27 mL, 25.0 mmol, 1.0 equiv) was added dropwise *via*

a syringe over 5 min. After gas evolution had ceased, a solution of PhSeBr (7.08 g, 30.0 mmol, 1.2 equiv) in THF (30 mL) was quickly added at 0 °C, resulting in a bright yellow solution. After 30 min, the reaction mixture was diluted with Et_2O (20 mL) and quenched with saturated $NaHCO_3$ (50 mL). The organic layer was separated and washed with 10% $NaHSO_3$ (2 × 50 mL), H_2O (3 × 50 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system (0 → 50% EtOAc/hexanes) to afford diethyl 2-methyl-2-(phenylselenyl)malonate which was carried on directly to the next step.

An oven-dried, 250-mL round-bottomed flask was charged with a solution of diethyl 2-methyl-2-(phenylselenyl)malonate in anhydrous CCl_4 (34 mL), followed by addition of H_2O_2 (35% in H_2O, 21.4 mL, 250 mmol, 10.0 equiv). The reaction temperature was maintained at ambient temperature (23 °C) using a water bath. After 2 h, H_2O (10 mL) was added to dissolve the white precipitate. The organic layer was then separated and the aqueous phase was extracted with anhydrous CCl_4 (3 × 10 mL), and the combined organics were dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation (without heating) to afford diethyl 2-methylenemalonate **5a** (4.1 g, 94% yield, light yellow liquid) of sufficient purity to be used directly in the next step (Note: purification of this unstable compound led to extensive loss of material on silica gel). The reactive malonate alkylidene **5a** was stored as a solution in anhydrous benzene (1.0 M) at –20 °C to prevent decomposition likely through polymerization. TLC (EtOAc:hexanes, 1:9 *v/v)*: R_f = 0.50; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.46 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.0, 135.2, 134.0, 61.5, 14.1. Other spectral data matched that previously reported.[35]

Dibenzyl 2-methylenemalonate (5b). Dibenzyl 2-methylmalonate **A1** was prepared by a modified literature procedure.[36] In an oven-dried, 250-mL round-bottomed flask, dibenzyl malonate (14.2 g, 50.0 mmol, 1.0 equiv) and anhydrous K_2CO_3 (8.3 g, 60.0 mmol, 1.2 equiv) were dissolved in anhydrous acetone (50 mL) and stirred at ambient temperature (23 °C) for 5 min, then iodomethane (3.73 mL, 60.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was refluxed (60-65 °C) for 20 h. Upon completion (as judged by TLC with complete consumption of dibenzyl malonate), the reaction mixture was diluted with Et_2O (50 mL) and filtered through a pad of celite (Et_2O wash). The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system (0 → 10% EtOAc/hexanes) to obtain dibenzyl 2-methylmalonate **A1** (12.6 g, 85% yield) as a clear liquid. Spectral data matched that previously reported.[37]

Dibenzyl 2-methylenemalonate **5b** was prepared by a modified literature procedure.[34] Into an oven-dried, 250-mL round-bottomed flask equipped with a stir bar was added NaH (60% suspension in mineral oil, 1.40 g, 35.0 mmol, 1.5 equiv) and then THF (80 mL) and the slurry was cooled to 0 °C under N_2. To the slurry was slowly added a solution of dibenzyl 2-methylmalonate **A1** (6.90 g, 23.3 mmol, 1.0 equiv) in THF (10 mL) *via* a syringe over 30 min using a syringe pump. After gas evolution had ceased (~ 5 min after complete addition of **A1** solution), a solution of PhSeBr (6.61 g, 28.0 mmol, 1.2 equiv) in THF (20 mL) was quickly added at 0 °C using a syringe over 2 min, resulting in a bright yellow solution. After 30 min, the reaction mixture was diluted with Et_2O (20 mL) and quenched with saturated $NaHCO_3$ (50 mL). The organic layer was separated and washed with 10% $NaHSO_3$ (2 × 50 mL), H_2O (3 × 50 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system (0 → 10% EtOAc/hexanes) to afford dibenzyl 2-methyl-2-(phenylselanyl)malonate and carried directly to the next step.

An 100-mL round-bottomed flask was charged with a solution of dibenzyl 2-methyl-2-(phenylselanyl)malonate in anhydrous CCl_4 (30 mL), followed by addition of H_2O_2 (35% in H_2O, 20.0 mL, 233 mmol, 10.0 equiv). The reaction temperature was maintained at ambient temperature (23 °C) using a water bath. After 2 h, H_2O (10 mL) was added to dissolve the white precipitate. The organic layer was then separated and the aqueous phase was extracted with anhydrous CCl_4 (3 × 10 mL), and the combined organics were dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation to afford pure dibenzyl 2-methylenemalonate **5b** (5.67 g, 83% yield, light yellow liquid) of sufficient purity to be used directly in the next step (Note: purification of this compound led to extensive loss of material on silica). The compound **5b** was stored as a solution in anhydrous benzene (1.0 M) at –20 °C to prevent decomposition. TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.80; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42-7.35 (m, 10H), 6.65 (s, 2H), 5.31 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.7 (2), 135.6 (2), 135.4, 134.5, 128.6 (4), 128.4 (2), 128.3 (4), 67.3 (2); **IR** (thin film): 3066, 3034, 2956, 1735, 1498, 1456 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{16}O_4Na$ $[M+Na]^+$: 319.0941; found 319.0929.

Representative procedure for Michael-Michael-aldol-β-lactonization delivering racemic β-lactone as described for bicyclic β-lactone 1a:

Triethyl (1*S*,6*S*)-5,6-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3,5-tricarboxylate ((±)-1a). An oven-dried, 10-mL round-bottomed flask was charged with a solution of LHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) and diluted with THF (0.5 mL) at -78 °C,

followed by slow, dropwise addition of a solution of β-ketoester **4a** (43 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL) by syringe over ~ 2 min. The resulting mixture was warmed to 0 °C and stirred for 30 min, then a solution of diester **5a** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv), diluted to 1.0 mL with THF, was added dropwise via a syringe over ~ 3 min. After 30 min at 0 °C, a solution of 4-PPY (9 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv), weighed out in a vial and diluted with CH_2Cl_2 (1.0 mL), was added via a syringe. A solution of acid chloride **3a** (41 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) was then added at 0 °C over 30 min by a syringe pump. The reaction temperature was maintained at 0 °C throughout the addition of **3a** and then the reaction was stirred at ambient temperature (23 °C) for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of 0 to 40% EtOAc/hexanes) to afford two separable 2 diastereomers of bicyclic-β-lactone **1a** (diastereomer A: 30 mg, 27% yield; diastereomer B: 30 mg, 27% yield;) as a yellow, viscous liquid. Diastereomer A: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.38. **^{1}H NMR** (500 MHz, benzene-d_6): δ 4.00 – 3.81 (m, 6H), 3.52 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.70 (dd, *J* = 6.3, 2.6 Hz, 1H), 2.61 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.52 (dd, *J* = 16.6, 6.3 Hz, 1H), 1.37 (s, 3H), 1.13 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.85 (app q, *J* = 7.1 Hz, 6H); **^{13}C NMR** (125 MHz, benzene-d_6) δ 172.6, 172.2, 171.2, 168.9, 78.7, 62.4, 62.0, 61.5, 54.3, 51.3, 47.9, 31.6, 23.5, 21.3, 20.2, 14.0, 13.9, 13.8. **IR** (thin film): 2983, 2940, 1828, 1731, 1449 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{26}O_8Na$ $[M+Na]^+$: 393.1520, found: 393.1506. Diastereomer B: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.32. **^{1}H NMR** (500 MHz, benzene-d_6): δ 4.00 – 3.81 (m, 6H), 3.52 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.70 (dd, *J* = 6.3, 2.6 Hz, 1H), 2.61 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.52 (dd, *J* = 16.6, 6.3 Hz, 1H), 1.37 (s, 3H), 1.13 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.85 (app q, *J* = 7.1 Hz, 6H); **^{13}C NMR** (125 MHz, benzene-d_6): δ 172.6, 172.2, 171.2, 168.9, 78.7, 62.4, 62.0, 61.5, 54.3, 51.3, 47.9, 31.6, 23.5, 21.3, 20.2, 14.0, 13.8, 13.8; **IR** (thin film): 2983, 2940, 1828, 1731, 1449 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{26}O_8Na$ $[M+Na]^+$: 393.1520, found: 393.1506.

Triethyl (1*S*,6*S*)-5-benzyl-6-methyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3,5-tricarboxylate ((±)-**1b**): Prepared according to the procedure described for compound **1a** using LHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), ethyl 2-benzylacetoacetate **4b** (66 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5a** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), a solution of 4-PPY (9 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), and a solution of acid chloride **3a** (41 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). After

20 h, the crude product was purified by an automated flash chromatography system (gradient of 0 to 40% EtOAc/hexanes) to afford a 1:1 diastereomeric mixture of bicyclic-β-lactone **1b** (117 mg, 75% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.37. **^{1}H NMR** (500 MHz, benzene-d_6): δ 7.10 – 6.94 (m, 5H), 4.00 – 3.76 (m, 6H), 3.22 (d, *J* = 15.9 Hz, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 2.93 (d, *J* = 13.5 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.70 – 2.63 (m, 2H), 2.61 – 2.51 (m, 1H), 1.48 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, benzene-d_6): δ 172.5, 172.2, 171.8, 171.17, 171.16, 170.9, 169.0, 168.6, 136.71, 136.69, 131.0, 130.0, 128.5, 128.35, 127.09, 126.94, 79.53, 79.43, 62.54, 62.46, 61.86, 61.76, 61.46, 61.08, 54.6, 52.69, 52.19, 52.09, 51.2, 40.3, 38.7, 31.8, 26.2, 24.3, 23.7, 22.6, 21.9, 13.91, 13.87, 13.80, 13.66, 13.54; **IR** (thin film): 2980, 2918, 2849, 1829, 1733, 1455 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{24}H_{30}O_8Na$ $[M+Na]^+$: 469.1833, found: 469.1818.

4,4-dibenzyl 5a-ethyl (2a*S*,3*S*,5a*R*,8a*S*)-3-methyl-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((±)-**1c**): Prepared according to the procedure for compound **1a** using LHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), a solution of (±)-HBTM **14** (16 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), and a solution of acid chloride **3b** (47 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). After 20 h, the crude product was purified by an automated flash chromatography system (gradient of 0 to 30% EtOAc/hexanes) to afford a single diasteremer (as judged by crude ^{1}H NMR) of tricyclic-β-lactone **1c** (34.3 mg, 22% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.50. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 – 7.22 (m, 10H), 5.21 (s, 2H), 5.13 (d, *J* = 4.3 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.26 (d, *J* = 11.6 Hz, 1H), 2.98 (d, *J* = 15.2 Hz, 1H), 2.82 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.60 (dt, *J* = 12.8, 6.6 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.10 – 1.84 (m, 2H), 1.74 – 1.55 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.1, 171.0, 170.8, 170.2, 135.3, 134.7, 128.83, 128.78 (4), 128.6 (2), 128.5, 128.4 (2), 87.3, 67.7, 67.6, 61.8, 57.5, 57.0, 52.5, 39.7, 39.0, 38.7, 33.7, 23.7, 16.8, 14.1; **IR** (thin film): 3065, 3034, 2963, 1828, 1729, 1498, 1455 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{30}H_{33}O_8$ $[M+H]^+$: 521.2175, found: 521.2159.

4,4-dibenzyl 3,5a-diethyl (2a*S*,3*S*,5a*R*,8a*S*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4,5a(5*H*,6*H*)-tetracarboxylate ((±)-**1d**): Prepared according to the procedure for compound **1a** using LHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a

solution of diester **5b** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), a solution of 4-PPY (9 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), and a solution of acid chloride **3c** (73 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). After 20 h, the crude product was purified by an automated flash chromatography system (gradient of 0 to 30% EtOAc/hexanes) to afford a single diasteremer (as judged by crude ^{1}H NMR) of tricyclic-β-lactone **1d** (56.3 mg, 32% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.42; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 5.19 (app s, 2H), 5.16, 5.12 (ABq, J_{AB} = 11.9 Hz, 2H), 4.15-4.04 (m, 4H), 4.02, 3.81 (ABq, J_{AB} = 9.6 Hz, 2H), 3.06 (d, *J* = 15.1 Hz, 1H), 2.67-2.62 (m, 1H), 2.41 (d, *J* = 15.1 Hz, 1H), 2.18-2.14 (m, 1H), 1.80-1.70 (m, 1H), 1.67-1.54 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.5, 170.3, 170.2, 169.3, 168.1, 135.0, 134.3, 129.1 (2), 128.9, 128.7 (2), 128.6 (2), 128.4, 128.2 (2), 85.7, 68.3, 68.1, 61.91, 61.90, 55.9, 52.7, 52.2, 43.3, 39.7, 39.3, 39.2, 23.3, 13.9, 13.8; **IR** (thin film): 2978, 1836, 1737, 1453, 1370 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{32}H_{35}O_{10}$ $[M+H]^+$: 579.2230, found: 579.2251.

Triethyl (2a*S*,5a*R*,8a*S*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((±)-**1e**): Prepared according to the procedure for compound **1a** using LHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5a** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), a solution of 4-PPY (9 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), and a solution of acid chloride **3a** (41 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). After 20 h, the crude product was purified by an automated flash chromatography system (gradient of 0 to 45% EtOAc/hexanes) to afford a single diasteremer (as judged by crude ^{1}H NMR) of tricyclic-β-lactone **1e** (66.4 mg, 58% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.47. **^{1}H NMR** (500 MHz, benzene-d_6): δ 3.99 – 3.90 (m, 4H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.32 (dd, *J* = 10.2, 9.3 Hz, 1H), 3.04 (d, *J* = 15.2 Hz, 1H), 2.76 (dd, *J* = 14.2, 10.2 Hz, 1H), 2.63 – 2.47 (m, 2H), 2.25 (dd, *J* = 15.2, 1.3 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.77 – 1.63 (m, 2H), 1.58 – 1.36 (m, 2H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, benzene-d_6): δ 172.9, 171.6, 170.7, 169.4, 85.3, 61.8, 61.8, 61.7, 52.7, 52.5, 51.2, 39.4, 39.0, 37.1, 27.0, 23.3, 13.9, 13.9, 13.9; **IR** (thin film): 2979, 2873, 1834, 1733, 1465, 1367 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{26}O_8Na$ $[M+Na]^+$: 405.1520, found: 405.1508.

Representative procedure for the enantioselective Michael-Michael-aldol-β-lactonization as described for 1c and 1d:

4,4-Dibenzyl 5a-ethyl (2a*S*,3*S*,5a*R*,8a*S*)-3-methyl-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((+)-1c). Into an oven-dried, 10-mL round-bottomed flask containing a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) at 0 °C, was added dropwise a solution of ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL) over ~ 2 min. The resulting mixture was stirred for 15 min at 0 °C, followed by a dropwise addition of a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) *via* syringe over ~ 2 min. After 15 min at 0 °C, a solution of (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added *via* syringe. A solution of acid chloride **3b** (38 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was then added at 0 °C over 5 h using a syringe pump. The reaction temperature was maintained at 0 °C throughout the addition of **3b** and then the reaction was stirred at this temperature for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^1H and ^{13}C NMR) of tricyclic-β-lactone **1c** (67 mg, 43% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.50. $[\alpha]_D^{23.3}$ +1.60 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 16.6 min, t_{major} = 18.4 min; 93.5:6.5 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of "enantiomeric" HBTM 2.1 catalyst. **^1H NMR** (500 MHz, $CDCl_3$): δ 7.43 – 7.22 (m, 10H), 5.21 (s, 2H), 5.13 (d, *J* = 4.3 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.26 (d, *J* = 11.6 Hz, 1H), 2.98 (d, *J* = 15.2 Hz, 1H), 2.82 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.60 (dt, *J* = 12.8, 6.6 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.10 – 1.84 (m, 2H), 1.74 – 1.55 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.1, 171.0, 170.8, 170.2, 135.3, 134.7, 128.83, 128.78 (4), 128.6 (2), 128.5, 128.4 (2), 87.3, 67.7, 67.6, 61.8, 57.5, 57.0, 52.5, 39.7, 39.0, 38.7, 33.7, 23.7, 16.8, 14.1; **IR** (thin film): 3065, 3034, 2963, 1828, 1729, 1498, 1455 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{30}H_{33}O_8$ $[M+H]^+$: 521.2175, found: 521.2159.

(2a*R*,3*R*,5a*S*,8a*R*)-4,4-Dibenzyl 3,5a-diethyl 2-oxohexahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4,5a(5*H*)-tetracarboxylate ((+)-1d). Following the representation procedure, into an oven-dried, 10-mL round-bottomed flask containing a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) at -20 °C, was added dropwise a solution of

ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL) over ~ 2 min. The resulting mixture was stirred for 15 min at -20 °C, followed by dropwise addition of a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) *via* syringe over ~ 2 min. After 15 min at -20 °C, a solution of (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was prepared in a vial and added *via* syringe. A solution of acid chloride **3c** (59 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was then added at -20 °C over 5 h using a syringe pump. The reaction temperature was maintained at -20 °C throughout the addition of **3c** and then the reaction was stirred at this temperature for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^1H and ^{13}C NMR) of tricyclic-β-lactone **1d** (107 mg, 61% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.42; $[\alpha]_D^{17}$ +3.49 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AS-H column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 11.7 min, t_{minor} = 18.0 min; 94:6 *er*. Absolute and relative stereochemistry were determined by amidation of β-lactone **1d** as indicated below. **^1H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 5.19 (app s, 2H), 5.16, 5.12 (ABq, J_{AB} = 11.9 Hz, 2H), 4.15-4.04 (m, 4H), 4.02, 3.81 (ABq, J_{AB} = 9.6 Hz, 2H), 3.06 (d, *J* = 15.1 Hz, 1H), 2.67-2.62 (m, 1H), 2.41 (d, *J* = 15.1 Hz, 1H), 2.18-2.14 (m, 1H), 1.80-1.70 (m, 1H), 1.67-1.54 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.5, 170.3, 170.2, 169.3, 168.1, 135.0, 134.3, 129.1 (2), 128.9, 128.7 (2), 128.6 (2), 128.4, 128.2 (2), 85.7, 68.3, 68.1, 61.91, 61.90, 55.9, 52.7, 52.2, 43.3, 39.7, 39.3, 39.2, 23.3, 13.9, 13.8; **IR** (thin film): 2978, 1836, 1737, 1453, 1370 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{32}H_{35}O_{10}$ $[M+H]^+$: 579.2230, found: 579.2251. Absolute stereochemistry was assigned by derivatization as described below.

Triethyl (2a*R*,5a*S*,8a*R*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((–)-1e). Prepared according to the procedure for compound **1d** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5a** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3a** (41 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was warmed to 23 °C and stirred for an additional 15 h and then

concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^{1}H and ^{13}C NMR) of tricyclic-β-lactone **1e** (44 mg, 39% yield) as a yellow, viscous liquid: Spectral data match with previously synthesized lactone **1e**. $[\alpha]_D^{22.5}$ = -12.13 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 99:1, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 42.0 min, t_{major} = 46.7 min; 66.5:33.5 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of the same (–)-BTM catalyst.

4,4-Dibenzyl 5a-ethyl (2a*R*,5a*S*,8a*R*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((–)-1f). Prepared according to the procedure for compound **1d** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3a** (41 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^{1}H and ^{13}C NMR) of tricyclic-β-lactone **1f** (29 mg, 19% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.47. $[\alpha]_D^{24.0}$ = -52.00 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AS-H column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 21.7 min, t_{major} = 27.5 min; 72:28 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of the same (–)-BTM catalyst. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 10H), 5.17 – 5.03 (m, 4H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.52 (dd, *J* = 10.2, 9.4 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H), 2.65 – 2.43 (m, 3H), 2.27 – 2.15 (m, 2H), 1.94 – 1.77 (m, 2H), 1.68 – 1.57 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.0, 171.2, 170.5, 170.0, 135.2, 134.8, 128.9, 128.8 (2), 128.70 (2), 128.67 (2), 128.6, 128.3 (2), 85.7, 68.0, 67.8, 61.8, 52.4, 52.3, 50.6, 39.3, 38.8, 36.6, 26.7, 23.1, 14.1. **IR** (thin film): 3064, 3034, 2927, 2871, 1832, 1732, 1498 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{29}H_{30}O_8Na$ $[M+Na]^+$: 529.1833, found: 529.1819.

Dibenzyl (2a*S*,3*S*,5a*S*,8a*S*)-5a-cyano-3-methyl-2-oxohexahydro-2*H*-indeno[3a,4-*b*]oxete-4,4(5*H*)-dicarboxylate ((+)-1g): Prepared according to the procedure for compound **1c** using

a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of cyclopentanone-2-carbonitrile **4d** (33 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3b** (38 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^1H and ^{13}C NMR) of tricyclic-β-lactone **1g** (35 mg, 25% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 4:6 *v/v,* Hanessian's stain): R_f = 0.53. $[\alpha]_D^{24.6}$ +13.33 (*c* = 0.68, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AS-H column: hexanes:*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 17.8 min, t_{minor} = 26.7min; 60.5:39.5 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of "enantiomeric" HBTM 2.1 catalyst. **^1H NMR** (500 MHz, $CDCl_3$): δ 7.42 – 7.18 (m, 10H), 5.23 (d, *J* = 12.1 Hz, 1H), 5.20 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.1 Hz, 1H), 3.31 (d, *J* = 8.3 Hz, 1H), 3.18 (dq, *J* = 8.4, 6.9 Hz, 1H), 2.80 (d, *J* = 15.3 Hz, 1H), 2.57 – 2.48 (m, 1H), 2.39 – 2.28 (m, 1H), 2.22 – 2.10 (m, 2H), 2.05 – 1.88 (m, 2H), 1.86 – 1.75 (m, 1H), 1.07 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.8, 169.6, 167.9, 134.9, 134.4, 128.92, 128.82 (2), 128.78 (2), 128.67 (2), 128.63, 128.60 (2), 119.8, 84.3, 68.3, 68.07, 58.1, 56.3, 41.9, 39.8, 37.1, 36.8, 32.1, 22.8, 17.4. **IR** (thin film): 3034, 2968, 1838, 1735, 1455, 1217 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{28}H_{27}NO_6Na$ $[M+Na]^+$: 496.1736, found: 496.1753.

4,4-Dibenzyl 3-ethyl (2a*R*,3*R*,5a*R*,8a*R*)-5a-cyano-2-oxohexahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4(5*H*)-tricarboxylate ((–)-1h): Prepared according to the procedure for compound **1d** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of cyclopentanone-2-carbonitrile **4d** (33 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3c** (59 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at -20 °C for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^1H and ^{13}C NMR) of tricyclic-β-lactone **1h** (41 mg, 26% yield) as a yellow,

viscous liquid: TLC (EtOAc:hexanes, 4:6 *v/v,* Hanessian's stain): R_f = 0.43. $[\alpha]_D^{25.2}$ = -13.87 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 14.98 min, t_{major} = 18.88 min; 79:21 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of the same (–)-BTM catalyst. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 – 7.16 (m, 10H), 5.29 (d, *J* = 12.1 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.05 (d, *J* = 12.1 Hz, 1H), 5.02 (d, *J* = 12.2 Hz, 1H), 4.09 – 3.91 (m, 4H), 2.92 (dd, *J* = 15.2, 1.2 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.46 – 2.34 (m, 1H), 2.29 (d, *J* = 15.2 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.02 – 1.91 (m, 2H), 1.90 – 1.81 (m, 1H), 1.21 (dt, *J* = 46.0, 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.3, 168.3, 168.0, 166.0, 134.57, 134.34, 128.98, 128.78 (2), 128.75 (2), 128.63 (2), 128.59, 128.41 (2), 119.8, 82.1, 68.80, 68.26, 62.5, 54.83, 54.25, 42.74, 42.59, 42.39, 39.0, 35.5, 23.0, 14.0. **IR** (thin film): 2964, 1844, 1737, 1454, 1372 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{30}H_{30}NO_8$ $[M+H]^+$: 532.1971, found: 532.1992.

4,4-Dibenzyl 5a-ethyl (2a*S*,3*S*,5a*R*,9a*S*)-3-methyl-2-oxohexahydronaphtho[8a,1-*b*]oxete-4,4,5a(2*H*,5*H*)-tricarboxylate ((+)-1i): Prepared according to the procedure for compound **1c** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclohexane-1-carboxylate **4f** (51 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3b** (38 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^{1}H and ^{13}C NMR) of tricyclic-β-lactone **1i** (44 mg, 27% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.35. $[\alpha]_D^{25.0}$ +8.13 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 18.0 min, t_{major} = 22.8 min; 82:18 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of "enantiomeric" HBTM 2.1 catalyst. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37 – 7.17 (m, 10H), 5.16 (d, *J* = 1.5 Hz, 2H), 5.15 – 5.03 (m, 2H), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.99 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.86 (d, *J* = 12.2 Hz, 1H), 2.76 – 2.68 (m, 2H), 2.59 (d, *J* = 15.4 Hz, 1H), 2.26 (ddd, *J* = 15.1, 13.5, 4.3 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.89 (m, 1H), 1.75 – 1.62 (m, 3H), 1.60 – 1.35 (m, 2H), 1.21 (t, *J* =

7.1 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.3, 171.6, 170.86, 170.13, 135.4, 134.7, 128.77, 128.62 (2), 128.59 (2), 128.54 (2), 128.51, 128.45 (2), 77.4, 67.76, 67.62, 61.7, 60.0, 57.2, 46.6, 36.4, 34.0, 32.9, 30.9, 21.2, 20.4, 17.6, 14.0. **IR** (thin film): 3034, 2939, 2866, 1823, 1727, 1455 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{31}H_{34}O_8Na$ $[M+Na]^+$: 557.2151, found: 557.2176.

4,4-Dibenzyl 3,5a-diethyl (2a*R*,3*R*,5a*S*,9a*R*)-2-oxohexahydronaphtho[8a,1-*b*]oxete-3,4,4,5a(2*H*,5*H*)-tetracarboxylate ((–)-1j): Prepared according to the procedure for compound **1d** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclohexane-1-carboxylate **4f** (51 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3c** (59 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at -20 °C for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^{1}H and ^{13}C NMR) of tricyclic-β-lactone **1j** (40 mg, 23% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.38. $[\alpha]_D^{25.0}$ = -41.47 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 47.7 min, t_{major} = 52.6 min; 94:6 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of the same (–)-BTM catalyst. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35 – 7.24 (m, 10H), 5.19 – 5.05 (m, 4H), 4.18 – 4.09 (m, 1H), 4.08 – 3.92 (m, 4H), 3.59 (d, *J* = 9.1 Hz, 1H), 2.76 (d, *J* = 15.7 Hz, 1H), 2.60 (d, *J* = 15.6 Hz, 1H), 2.00 (ddd, *J* = 14.3, 9.8, 3.7 Hz, 2H), 1.89 – 1.80 (m, 1H), 1.67 (ddd, *J* = 14.6, 10.5, 4.3 Hz, 1H), 1.61 – 1.48 (m, 2H), 1.47 – 1.20 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.6, 170.98, 170.48, 170.32, 168.2, 135.0, 134.7, 128.88, 128.78 (2), 128.71 (2), 128.67 (2), 128.60, 128.52 (2), 77.2, 68.39, 68.37, 61.88, 61.76, 55.9, 55.1, 46.6, 42.0, 35.1, 34.4, 31.7, 21.5, 20.6, 14.03, 14.00. **IR** (thin film): 3065, 3034, 2939, 2867, 1834, 1731, 1498 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{33}H_{36}O_{10}Na$ $[M+Na]^+$: 615.2201, found: 615.2181.

Dibenzyl (2a*S*,3*S*,5a*R*,8a*S*)-3-methyl-2-oxo-5a-(phenylsulfonyl)hexahydro-2*H*-indeno[3a,4-*b*]oxete-4,4(5*H*)-dicarboxylate ((+)-1k): Prepared according to the procedure for compound **1c** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of 2-(phenylsulfonyl)cyclopentan-1-one[38] **4e** (67 mg, 0.30

mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3b** (47 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was warmed to 23 °C and stirred for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^1H and ^{13}C NMR) of tricyclic-β-lactone **1k** (54 mg, 32% yield) as a light yellow solid: m.p. 74 – 75 °C. TLC (Et_2O:hexanes, 8:2 *v/v,* Hanessian's stain): R_f = 0.59; $[\alpha]_D^{22.6}$ = +15.60 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 71.8 min, t_{major} = 75.5 min; 85.5:14.5 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of "enantiomeric" HBTM 2.1 catalyst. **^1H NMR** (600 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.15 (m, 10H), 5.20 – 5.02 (m, 4H), 3.40 (d, *J* = 11.4 Hz, 1H), 3.11 (d, *J* = 15.3 Hz, 1H), 2.80 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.49 (d, *J* = 15.4 Hz, 1H), 2.41 – 2.26 (m, 2H), 1.80 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.68 (dt, *J* = 14.4, 6.9 Hz, 1H), 1.58 (dp, *J* = 14.1, 7.1 Hz, 1H), 1.35 – 1.24 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.68, 169.39, 168.7, 136.7, 134.66, 134.24, 134.17, 131.6 (2), 129.12 (2), 128.99, 128.80, 128.78 (2), 128.77 (2), 128.75 (2), 128.58 (2), 83.9, 70.5, 68.08, 67.86, 60.0, 56.5, 40.2, 39.1, 38.6, 35.1, 21.7, 16.0. **IR** (thin film): 3065, 3034, 2966, 2885, 1833, 1730, 1650, 1498 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{33}H_{32}O_8SNa$ $[M+Na]^+$: 611.1710, found: 611.1705.

4,4-Dibenzyl 3-ethyl (2a*S*,3*S*,5a*R*,8a*S*)-2-oxo-5a-(phenylsulfonyl)hexahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4(5*H*)-tricarboxylate ((+)-1l): Prepared according to the procedure for compound **1c** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of 2-(phenylsulfonyl)cyclopentan-1-one[38] **4e** (67 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3c** (73 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was warmed to 23 °C and stirred for an additional 15 h. The reaction was then concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by ^1H and ^{13}C NMR) of tricyclic-β-lactone **1l** (101 mg, 52% yield) as a light yellow solid: m.p. = 81 – 82 °C. TLC

(EtOAc:hexanes, 4:6 *v/v,* Hanessian's stain): R_f = 0.47. $[\alpha]_D^{25.0}$ = +33.87 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 60:40, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 11.5 min, t_{minor} = 13.98 min; 89:11 *er*. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of "enantiomeric" HBTM 2.1 catalyst. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.93 – 7.90 (m, 2H), 7.59 (td, *J* = 7.4, 1.3 Hz, 1H), 7.43 – 7.27 (m, 12H), 5.26 – 5.06 (m, 4H), 4.05 – 4.02 (m, 2H), 3.56 (d, *J* = 10.1 Hz, 1H), 3.24 – 3.15 (m, 1H), 2.79 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.24 (dd, *J* = 13.9, 6.6 Hz, 1H), 1.85 (dt, *J* = 13.5, 6.6 Hz, 1H), 1.65 – 1.58 (m, 3H), 1.40 – 1.24 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.54, 169.30, 168.5, 166.7, 136.8, 134.8, 134.23, 134.03, 131.6 (2), 129.34 (2), 129.14, 128.84, 128.82 (2), 128.79 (2), 128.74 (2), 128.53 (2), 83.5, 70.3, 68.72, 68.52, 62.2, 56.2, 54.8, 43.3, 40.3, 39.5, 37.9, 21.9, 14.0. **IR** (thin film): 2977, 1842, 1737, 1447 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{35}H_{34}O_{10}SLi$ $[M+Li]^+$: 653.2033, found: 653.2025.

Allyl benzyl malonate (A2). In an oven dried, 100-mL round-bottomed flash, monobenzyl malonate (6.0 g, 31 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. Oxalyl chloride (10.5 mL, 124 mmol, 4.0 equiv) was added dropwise followed by one drop of DMF. After 1 h, the ice bath was removed and the reaction mixture was stirred for 15 h. Excess oxalyl chloride was removed by azeotroping with benzene (3 x 10 mL). The crude product was concentrated by rotary evaporation and carried on directly to the next step.

In an oven dried, 250-mL round-bottomed flask, the crude product in the previous step (30.9 mmol, 1.0 equiv) and allyl alcohol (2.52 mL, 37.1 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (6.5 mL, 46 mmol, 1.5 equiv) was added dropwise over 30 min. The ice bath was removed and solution was stirred for 1 h. The reaction was quenched with water (30 mL). The organic layer was isolated and washed with saturated $NaHCO_3$ (3 x 45 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation to afford 4.6 g (>99% yield) of **A2** which was of sufficient purity to be carried on to the next step without purification. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 5H), 6.00 – 5.84 (m, 1H), 5.34 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.20 (s, 2H), 4.65 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.47 (s, 2H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 166.24, 166.03, 135.23, 131.45, 128.56 (2), 128.40 (2), 128.29, 118.74, 67.19, 66.04, 41.46.

1-Allyl 3-benzyl 2-methylmalonate (A3): An oven-dried round-bottomed flask was charged with allyl benzyl malonate (2.24 g, 9.59 mmol, 1.0 equiv), anhydrous K_2CO_3 (2.65 g, 19.2 mmol, 2.0 equiv), and anhydrous acetone (56 mL). The reaction mixture was stirred at ambient temperature (23 °C) for 10 min before iodomethane was added dropwise to the reaction mix-

ture. The reaction was refluxed for 40 h. Upon completion (as judged by TLC, disappeareance of **A2**), the reaction was filtered and concentrated to give **A3** (2.1 g, 89% yield) which was of sufficient purity to be carried on to the next step without purification. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 5H), 5.92 – 5.80 (m, 1H), 5.35 – 5.27 (m, 1H), 5.22 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.18 (dd, *J* = 16.4, 2.1 Hz, 3H), 4.62 (m, 1H), 3.56 (m, 1H), 1.48 (dd, *J* = 7.3, 1.8 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 169.77, 169.58, 135.4, 131.6, 128.53 (2), 128.29 (2), 128.10, 118.5, 67.1, 65.9, 46.1, 13.6.

1-Allyl 3-benzyl 2-methylenemalonate (5c): Prepared according to the procedure for preparation of compound **5b** using NaH (0.48 g, 12 mmol, 1.5 equiv), a solution of **A3** (2.0 g, 8.1 mmol, 1.0 equiv) in THF (5 mL), a solution of PhSeBr (2.3 g, 9.7 mmol, 1.2 equiv) in THF (10 mL). The reaction was concentrated and the crude mixture was purified by automated flash chromatography (0 to 5% EtOAc:hexane) to deliver 1-allyl 3-benzyl 2-methyl-2-(phenylselanyl)malonate which was carried on directly to the next step.

An oven-dried, 100-mL round-bottomed flask was charged with a solution of 1-allyl 3-benzyl 2-methyl-2-(phenylselanyl)malonate in anhydrous benzene (8 mL), followed by addition of H_2O_2 (35% in H_2O, 14.0 mL, 162 mmol, 20.0 equiv). The reaction temperature was maintained at ambient temperature (23 °C) using a water bath. After 2 h, H_2O (10 mL) was added to dissolve the white precipitate. The organic layer was then separated, washed with H_2O, and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation to afford pure **5c** (1.4 g, 70% yield over 2 steps, light yellow liquid) of sufficient purity to be used directly in the next step (Note: purification of this compound led to extensive loss of material on silica likely due to facile polymerization). The compound **5c** was stored as a solution in anhydrous benzene (1.0 M) at –20 °C to slow decomposition. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H), 6.58 (s, 2H), 5.93 (m, 1H), 5.42 – 5.14 (m, 4H), 4.71 (dt, *J* = 5.7, 1.5 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 163.51, 163.32, 135.32, 135.19, 134.4, 131.5, 128.50 (2), 128.29 (2), 128.10, 118.6, 67.1, 65.9.

4-Allyl 4-benzyl 3,5a-diethyl (2a*R*,3*R*,5a*S*,8a*R*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4,5a(5*H*,6*H*)-tetracarboxylate ((–)-1m). Prepared according to the representative procedure described for compound **1d** using a solution of LHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclopentanecarboxylate **4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **5c** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **3c** (73 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at -20

°C for an additional 15 h. 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 1:1 mixture of inseparable diastereomers of tricyclic-β-lactone **1m** (83 mg, 52% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 3:7 *v/v,* Hanessian's stain): R_f = 0.44. $[\alpha]_D^{24.7}$ -40.40 (*c* = 1.0, $CHCl_3$). NMR data is reported for the mixture of diastereomers (1:1): **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 – 7.26 (m, 10H), 5.92 – 5.75 (m, 2H), 5.35 – 5.07 (m, 8H), 4.64 (d, *J* = 5.8 Hz, 2H), 4.60 (d, *J* = 5.9 Hz, 2H), 4.22 – 3.96 (m, 10H), 3.79 (dd, *J* = 9.5, 0.6 Hz, 1H), 3.76 (dd, *J* = 9.6, 0.6 Hz, 1H), 3.07 (d, *J* = 15.1 Hz, 1H), 3.04 (d, *J* = 15.1 Hz, 1H), 2.74 – 2.58 (m, 2H), 2.40 (d, *J* = 15.0 Hz, 1H), 2.39 (d, *J* = 15.1 Hz, 1H), 2.37 – 2.09 (m, 2H), 1.95 – 1.79 (m, 2H), 1.80 – 1.49 (m, 6H), 1.30 – 1.16 (m, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.64, 172.62, 170.41, 170.39, 170.30 (2), 169.38, 169.31, 168.18, 168.16, 135.1, 134.5, 131.4, 130.9, 129.22, 129.16, 128.97, 128.78, 128.66, 128.64, 128.60, 128.53, 128.35, 128.30, 120.1, 118.9, 85.81, 85.79, 68.4, 68.2, 67.09, 66.99, 62.02, 61.99, 55.94, 55.86, 53.0, 52.8, 52.36, 52.32, 43.35 (2), 39.83 (2), 39.69, 39.47 (2), 39.43, 39.34, 39.1, 23.46, 23.41, 14.05, 14.01 (2), 13.96. **IR** (thin film): 2981, 1836, 1738, 1453 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{28}H_{32}O_{10}Na$ $[M+Na]^+$: 551.1888, found: 551.1843. Absolute stereochemistry was tentatively assigned by analogy to β-lactone **1d** *via* the use of the same (–)-BTM catalyst.

5-Allyl 5-benzyl 3a,6-diethyl (3a*S*,6*R*,7*R*,7a*R*)-7-((4-bromobenzyl)carbamoyl)-7a-hydroxyhexahydro-5*H*-indene-3a,5,5,6(4*H*)-tetracarboxylate (**16**). Into an oven-dried, 1-dram vial containing a solution of β-lactone (–)-**1m** (30 mg, 0.057 mmol, 1.0 equiv) in THF (1 mL), was added dropwise 4-bromobenzylamine (29 µL, 0.23 mmol, 4.0 equiv). The reaction was allowed to stir at ambient temperature (23 °C) for 20 h. Upon completion (as judged by TLC, disappearance of β-lactone **1m**), the reaction was concentrated by rotary evaporation and purified by an automated flash chromatography system (gradient of Et_2O/hexanes) to afford a 1:1 diastereomeric mixture of bicyclic amide **16** (26 mg, 62% yield) as a white solid: TLC (Et_2O:hexanes, 6:4 *v/v,* Hanessian's stain): R_f = 0.38; NMR data is reported as a 1:1 diastereomeric mixture of bicyclic amide **16: ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 – 7.43 (m, 4H), 7.35 – 7.28 (m, 10H), 7.20 (t, *J* = 8.2 Hz, 4H), 6.57 (t, *J* = 5.9 Hz, 1H), 6.43 (t, *J* = 5.8 Hz, 1H), 5.81 (m, 2H), 5.29 (m, 2H), 5.26 – 5.08 (m, 8H), 4.63 – 4.52 (m, 4H), 4.48 (app dt, *J* = 14.9, 5.7 Hz, 2H), 4.34 (app ddd, *J* = 15.4, 10.3, 5.5 Hz, 2H), 4.23 – 4.06 (m, 4H), 4.03 – 3.89 (m, 4H), 3.89 – 3.81 (m, 2H), 2.99 (d, *J* = 14.9 Hz, 1H), 2.93 (d, *J* = 14.8 Hz, 1H), 2.62 (d, *J* = 11.9 Hz, 1H), 2.55 (d, *J* = 12.0 Hz, 1H), 2.44 (d, *J* = 11.5 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H), 2.14 – 1.29 (m, 12H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.11 (app dt, *J* = 20.1, 7.1 Hz, 6H); **^{13}C NMR** (150 MHz; $CDCl_3$): δ 175.7, 175.4, 173.1, 172.9, 172.2, 171.97, 170.60, 170.54, 170.26, 170.16, 137.15, 137.09,

135.2, 134.8, 131.81 (2), 131.80 (2), 131.5, 131.1, 129.8, 129.73, 129.71 (2), 128.82 (2), 128.72, 128.67, 128.64 (2), 128.62, 128.49, 128.35 (2), 121.46, 121.41, 119.3, 118.9, 80.38, 80.24, 67.95, 67.93, 67.88, 67.83, 66.85, 66.76, 61.48, 61.43, 56.81, 56.75, 54.38, 54.29, 48.85, 48.34, 44.79, 44.55, 43.33, 43.23, 35.89, 35.58, 33.22, 33.04, 32.70, 31.68, 29.8 (2), 20.0, 19.8, 14.2, 13.9; **IR** (ATR): 3364, 3068, 2981, 2931, 2856, 1725, 1647, 1543 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{35}H_{41}BrNO_{10}$ $[M+H]^+$: 714.1910; found 714.1908.

5-Benzyl 3a,6-diethyl (3a*S*,5*S*,6*S*,7*R*,7a*R*)-7-((4-bromobenzyl)carbamoyl)-7a-hydroxyoctahydro-3a*H*-indene-3a,5,6-tricarboxylate ((+)-17). An oven-dried, 10-mL microwave vial containing a solution of amide **16** (21.4 mg, 0.0300 mmol, 1.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.0 mg, 0.0030 mmol, 10 mol%), PPh_3 (0.4 mg, 0.0015 mmol, 5.0 mol %), and HCO_2NH_4 (7.6 mg, 0.12 mmol, 4.0 equiv) in CH_3CN (0.6 mL) was degassed with Ar (3 times) and then heated in a microwave reactor at 100 °C for 2 h. Upon completion (as judged by TLC by disappearance of **16**), the reaction was concentrated by rotary evaporation and purified by flash chromatography (gradient of Et_2O/hexanes) to afford a 12:1 diastereomeric mixture of bicyclic amide (+)-**17** (17.8 mg, 94% yield) as a clear yellow liquid: TLC (Et_2O:hexanes, 8:2 *v/v,* Hanessian's stain): R_f = 0.44; $[\alpha]_D^{22.5}$ +4.27 (*c* = 0.5, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 60.8 min, t_{major} = 66.7 min; 97:3 *er*. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.24 (m, 9H), 6.21 (t, *J* = 5.6 Hz, 1H), 5.57 (s, 1H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 4.55 (dd, *J* = 14.7, 6.3 Hz, 0H), 4.48 (dd, *J* = 14.6, 5.8 Hz, 1H), 4.35 (dd, *J* = 14.6, 5.3 Hz, 1H), 4.21 (qd, *J* = 7.1, 1.8 Hz, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.65 (ddd, *J* = 11.8, 5.6, 3.8 Hz, 1H), 3.47 (ddd, *J* = 5.4, 3.9, 1.1 Hz, 1H), 3.08 (d, *J* = 3.9 Hz, 1H), 2.70 (ddd, *J* = 14.7, 3.9, 1.3 Hz, 1H), 2.28 – 2.16 (m, 1H), 2.02 – 1.57 (m, 6H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 177.1, 173.5, 173.1, 172.6, 138.0, 136.1, 128.81 (2), 128.55 (2), 128.34 (2), 128.22, 128.06 (2), 127.6, 81.9, 66.4, 61.63, 61.26, 53.3, 49.8, 44.0, 43.2, 37.9, 37.6, 37.2, 29.3, 19.7, 14.12, 14.10; **IR** (ATR): 3362, 3064, 3032, 2977, 2928, 1724, 1649, 1539, 1454 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{31}H_{37}BrNO_8$ $[M+H]^+$: 630.1697; found 630.1655.

ASSOCIATED CONTENT

Supporting Information

Analytical data including chiral HPLC traces and copies of ^{1}H and ^{13}C spectra for all new compounds.

AUTHOR INFORMATION

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Author Contributions

D.R. and K.N.V. conceived and developed the three-component MMAL process and K.N.V performed all experiments. D.R. and K.N.V composed the manuscript.

Notes

The authors declare no competing financial interest.

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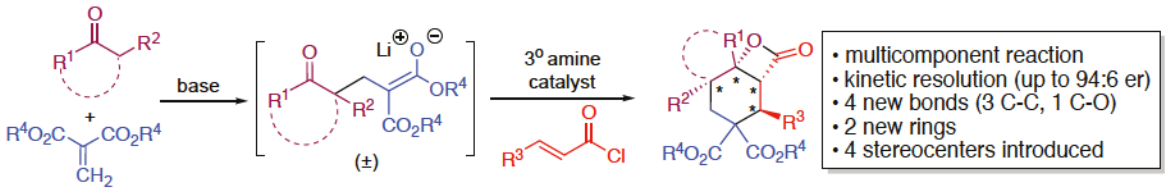
TOC Entry


base
3° amine
catalyst
(±)
• multicomponent reaction
• kinetic resolution (up to 94:6 er)
• 4 new bonds (3 C-C, 1 C-O)
• 2 new rings
• 4 stereocenters introduced