JOC The Journal of Organic Chemistry

Article

Diastereo- and Enantioselective Synthesis of Bi- and Tricyclic N-Heterocycle-Fused #-Lactones

Weixu Kong, and Daniel Romo

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02235 • Publication Date (Web): 10 Nov 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Diastereo- and Enantioselective Synthesis of Bi- and Tricyclic *N*-Heterocycle-Fused β-Lactones

Weixu Kong[‡] *and Daniel Romo*[*,†,‡]

[‡]*Department of Chemistry & Biochemistry, Baylor University, Waco, TX 76710.* [†]*Department of Chemistry, Texas A&M University, College Station, TX 77840.*

Email: daniel_romo@baylor.edu

Abstract

The utility of the nucleophile-catalyzed (Lewis base) aldol lactonization (NCAL) process for the diastereo- and enantioselective synthesis of *N*-heterocycle-fused-β-lactones from *N*-linked ketoacids is described. A series of bi- and tricyclic, *N*-heterocycle-fused, β-lactones were first synthesized in racemic fashion via the NCAL process with excellent diastereoselectivity (>19:1) utilizing 4-pyrrolidinopyridine as an effective achiral Lewis base. A catalytic, enantioselective version of this NCAL process using isothiourea catalysts provided access to bicyclic β-lactone-fused, *N*-heterocycles in moderate to good yields (up to 80%) with high enantiocontrol (up to >99:1 er). An unusual diastereodivergent NCAL process was discovered that leads to two different products; a tricyclic *N*-heterocycle-fused β-lactone and a bicyclic enamine derived from *in situ* decarboxylation of the diastereomeric tricyclic β-lactone. The reactivity of these adducts was briefly explored.

Introduction

As a class of unique oxygen-containing, strained heterocycles, β-lactones are not only versatile intermediates in synthetic chemistry[1,2] but are gaining increased use as tools for probing cellular function of enzymes and proteins with nucleophilic residues.[3-5] Our group first reported the catalytic, asymmetric intramolecular, nucleophile (Lewis base) catalyzed aldol lactonization

(NCAL) process of aldehyde acids in 2001[6] building on the elegant work of Wynberg[7] which makes use of *in situ* generated ammonium enolate intermediates[2,8] to deliver carbocycle-fused, bicyclic β-lactones. The NCAL process was subsequently extended to keto acids leading to a variety of bi- and tricyclic carbocycle-fused β-lactones[9] and was applied to the synthesis of several natural products by our group[10,11] and others.[12,13] In addition, we also applied the NCAL reaction to the synthesis of oxygen heterocycle-fused β-lactones.[14] We returned to the original inspiration for development of the NCAL process, namely the structure of the proteasome inhibitors omuralide and salinosporamide, and considered application of the NCAL process to *N*-heterocycle-fused β-lactones. Following application of the NCAL process to a racemic synthesis of a γ-lactam-fused β-toward (±)-salinosporamide A, we described a diastereoselective synthesis of this same γ-lactam-fused-β-lactone employing substrate control from a chiral ketoacid precursor leading to a bioinspired, 9-step enantioselective, synthesis of (+)-salinosporamide A from *R*-(–)-*O*-Bn serine.[15] The Dikshit group described application of the NCAL to *N*-linked aldehyde acids for the enantioselective synthesis of pyrrolidine- and piperidine-fused-β-lactones employing cinchona alkaloid Lewis bases.[16] Herein, we describe application of the NCAL process to *N*-linked keto acids for the diastereo- and enantioselective synthesis of bi- and tricyclic *N*-heterocycle-fused β-lactones **8** including several that are substructures or potential precursors to substructures of natural products (Figure 1).

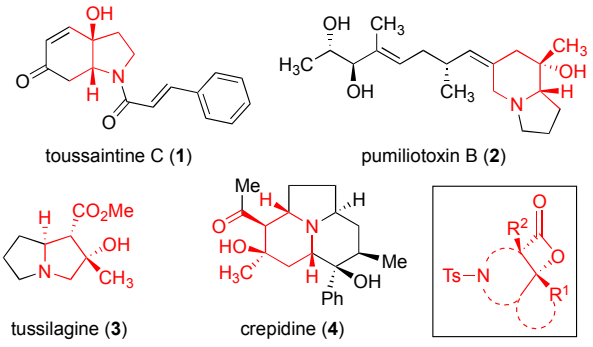
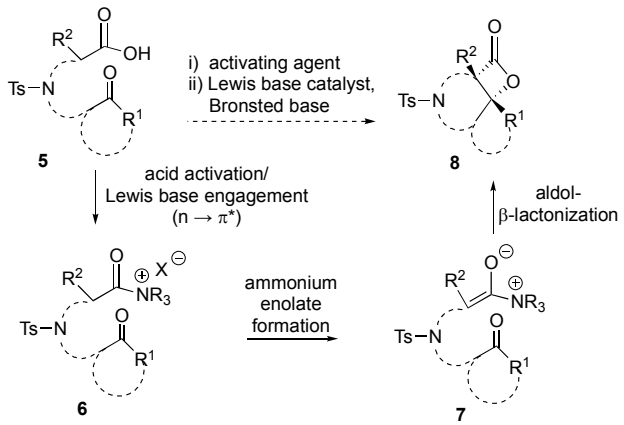


Figure 1. General structure of bi- and tricyclic *N*-heterocycle-fused β-lactones (inset) available through the described nucleophile (Lewis base)-catalyzed, aldol-lactonization (NCAL) process described herein and potentially useful for accessing various substructures (red) of natural products.

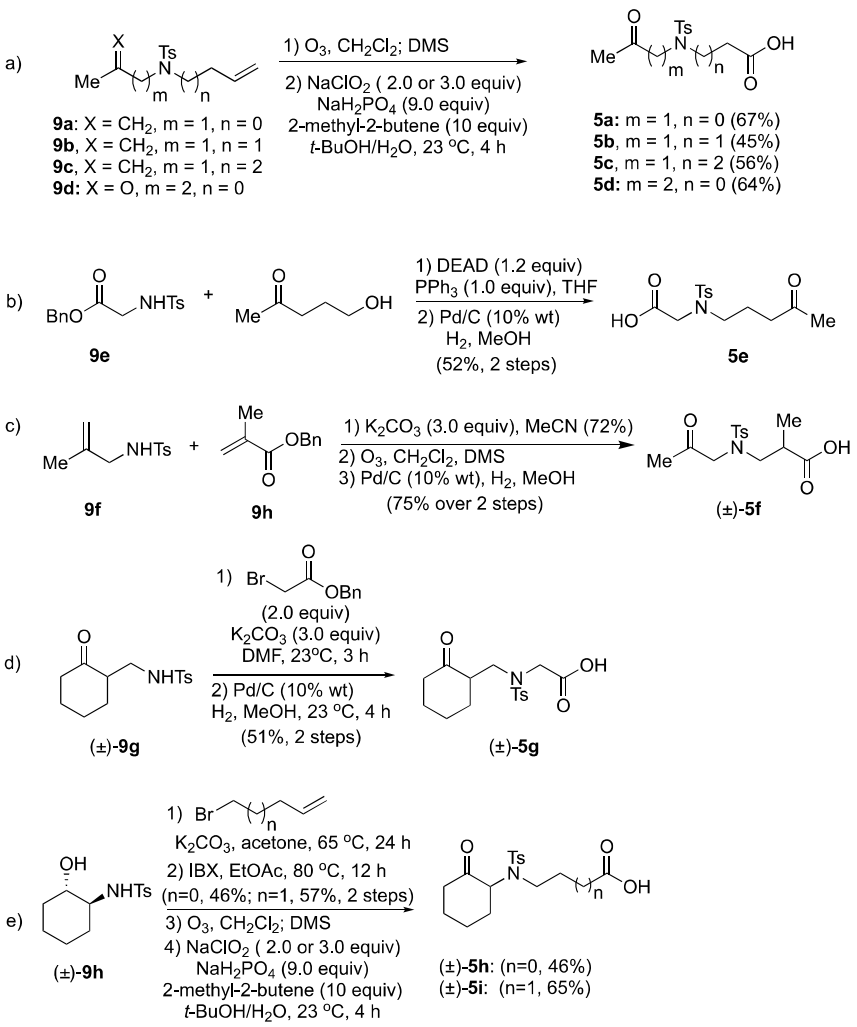
Mechanistically, the aldol-β-lactonization of *N*-linked keto acids towards *N*-heterocycle-fused-β-lactones would be derived through carboxylic acid activation and use of a chiral Lewis base in the presence of a Brønsted base (Scheme 1). Activation of the carboxylic acid by use of various activating agents, such as *p*-toluenesulfonyl chloride[9,17,18] and modified Mukaiyama's reagent,[16,19] enables engagement by a chiral Lewis base through an initial n→π* mode of interaction[20, 8] to ultimately form an acylammonium salt intermediate **6**. Deprotonation by the Brønsted base leads to ammonium enolate **7** which then undergoes a thermodynamically controlled *syn*-aldol reaction, since the *anti*-aldol cannot lactonize, followed by β-lactonization to afford β-lactone **8**. Although ketene formation is possible under these reaction conditions *via* elimination of acylammonium salt **6** enabling a possible racemic, [2+2] cycloaddition pathway to the β-lactone, the nucleophilicity of the Lewis base, slow elimination to ketene, and thus low concentration of ketene at ambient temperature presumably allows the NCAL process to be the prevalent pathway.[21]



Scheme 1. The catalytic, enantioselective, nucleophile (Lewis base)-catalyzed aldol-lactonization (NCAL) process to nitrogen-heterocycle-fused β-lactones **8** from *N*-linked keto acids **5**.

Results and Discussion

A series of *N*-linked keto acid substrates to be studied in the NCAL process were prepared through various synthetic routes (Scheme 2). A sequential ozonolysis/Pinnick oxidation of known terminal alkenes **9a-c**[22] and **9d**[23] led to keto acids **5a-d** in good yield (45-67%, 2 steps, Scheme 2a). Keto acid **5e** was prepared via a Mitsunobu reaction/hydrogenolysis sequence from known *N*-Ts aminoester **9e**[24] and 1-hydroxy-4-pentanone in 52% yield (2 steps, Scheme 2b). An aza-Michael reaction of *N*-Ts allylic amine **9f**[25] and benzyl methacrylate followed by ozonolysis and hydrogenolysis generated keto acid (±)-**5f** (Scheme 2c). The synthesis of cyclic keto acid substrates **5g-i** to access tricyclic β-lactones began with amino cyclohexanone **9g**[26] and amino alcohol **9h**[27] (Schemes 2d, 2e). Keto acid **5g** was obtained from amino ketone **9g** in a 2-step sequence involving *N*-alkylation and hydrogenolysis while a 4-step sequence delivered keto acids **5h** and **5i** from β-amino alcohol **9h**.

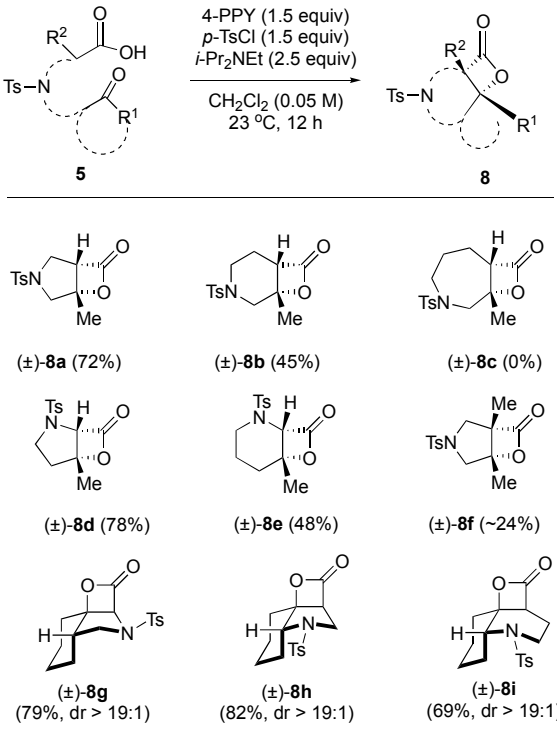


Scheme 2 Synthesis of ketoacids **5a-i** as substrates for the NCAL process leading to bi- and tricyclic, *N*-heterocycle fused β-lactones

With scalable access to *N*-linked keto acids **5a-i**, we first explored the NCAL process towards racemic *N*-heterocycle-fused-β-lactones synthesis employing 4-pyrrolidinopyridine (4-PPY) as Lewis base (Table 1). Under typical NCAL conditions employed previously for carbocycle-fused β-lactones, with inexpensive *p*-toluenesulfonyl chloride as a carboxylic acid activating agent,[18] keto acids **5a-i** delivered the corresponding *N*-heterocycle-fused, β-lactones **8**. Pyrrolidine-fused β-lactones (**8a**, **8d**, **8g**, **8h**) were obtained in yields ranging from 72-82%. The sterically congested bis-quaternary center containing pyrrolidine **8f** could also be obtained but in only ~24% yield. Generally, piperidine-fused β-lactones (**8b**, **8e**, **8i**) were formed in lower yields (45-69%) compared to pyrrolidine-fused systems as previously observed in the carbocyclic series likely reflecting the kinetic differences in 5 vs 6-membered ring formation and lower stability of

6-membered ring-fused β-lactones.[19] The *N*-tosyl protecting group was found to be optimal for these reactions after a brief screen since other protecting groups (*e.g.* carbamates) led to mostly recovered starting material. In addition, use of a tosyl group facilitated synthesis of substrates for example through aza-Michael additions (*cf.* Scheme 2c). An attempt was made to prepare the azepane-fused β-lactone **8c** however this did not provide detectable amounts of β-lactone. The tricyclic β-lactones **8g, h** were obtained in high diastereoselectivity (>19:1) and the relative stereochemistry shown for these adducts is supported by 2D NMR studies of pyrrolidine-fused, tricyclic β-lactone **8h** (see SI for details).

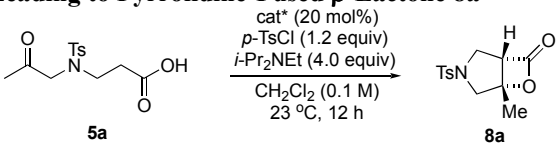
Table 1. Synthesis of Racemic *N*-Heterocycle-Fused β-Lactones 8 via the NCAL Process with 4-PPY as Lewis Base



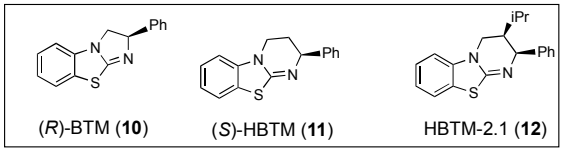
We next studied the enantioselective NCAL for the synthesis of *N*-heterocycle-fused β-lactones (NCAL) and keto acid **5a** was utilized for initial screening of catalysts and conditions. The chiral isothiourea catalysts benzotetramisole (BTM, **10**) and homobenzotetramisole (HBTM, **11)** developed by Birman[28,29] and HBTM 2.1 (**12**) developed by Smith[30] have served as excellent Lewis bases for the *in situ* preparation of chiral ammonium enolates[9,10,31-34] and more recently

unsaturated acylammonium enolates.[35] We therefore studied these Lewis bases initially and found that (*S*)-HBTM provided the best enantiomeric ratios among these catalysts (Table 2, entries 1-3) providing a 98:2 er albeit in low yield (34%). We studied the use of K_2CO_3 as stoichiometric insoluble base with the use of Hünig's base as a shuttle base[36-39] (Table 2, entry 4), however this did not improve the yield dramatically. Crude ^{1}H NMR analysis of these initial reactions and considering mass recovery before and after chromatographic purification suggested that some loss of β-lactone product was likely occurring on silica gel through possible acylation. We considered that excess Hünig's base present in the crude reaction mixture could promote β-lactone acylation of silica gel, so excess amounts were removed from the crude reaction mixture (confirmed by crude ^{1}H NMR) by aqueous extraction prior to purification by automated flash chromatography. This led to an improvement in yield from 36 to 44% of β-lactone **8a** (Table 2, entry 5). Furthermore, use of normal flash chromatography instead of automated flash chromatography led to a further improvement to 52% likely due to the smaller particle size and increased surface area of the prepacked columns (Table 2, entry 5). We determined that use of the shuttle base was not responsible for major yield improvements but rather the method of purification was key and thus subsequent reactions only employed Hünig's base and normal flash chromatography. The use of LiCl as additive was investigated next, given the utility in related reactions,[9,40] which led to a major improvement in yield to 78% with 99:1 er.

Table 2. Optimization of the Enantioselective NCAL Leading to Pyrrolidine-Fused β-Lactone 8a[a]



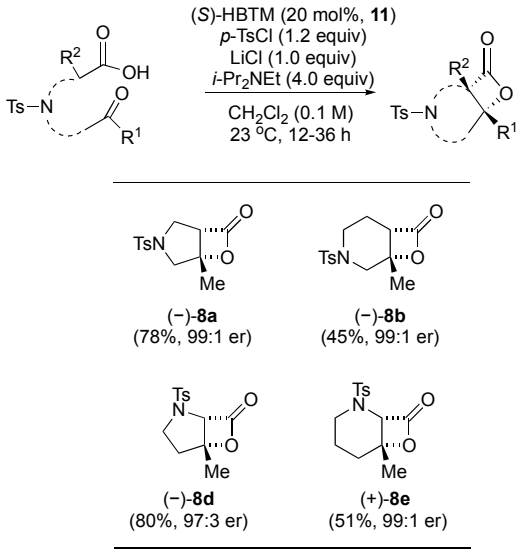
entry	cat.	additive	% yield[b]	er[c]
1	**10**	-	12[d]	85:15
2	**11**	-	34[d]	98:2
3	**12**		trace[d]	ND
4	**11**	K_2CO_3	36,[d] 44,[e] 52[f]	99:1
5	**11**	LiCl	78[e]	99:1



[a]The keto acid **5a** was added by syringe pump to the reaction mixture over 6 h. [b]Yields refer to isolated and purified pyrrolidine **8a**. [c] Determined by chiral HPLC analysis. [d]Purification involved concentration of the crude reaction mixture and direct loading on an automated flash chromatograph silica column. [e]An aqueous workup was performed to remove excess Hünig's base prior to purification by normal flash chromatography. [f]An aqueous workup was performed to remove excess Hünig's base prior to loading on an automated flash chromatography silica column. (er = enantiomeric ratio; ND = not determined)

With optimized conditions in hand, a brief survey of the scope of this NCAL process was explored with various *N*-linked keto acids (Table 3). For most bicyclic β-lactones (**8a**, **8b**, **8d**, **8e**), the yields were comparable to the corresponding racemic NCAL and the enantiomeric ratios were excellent (97:3 to 99:1). However, attempts to prepare β-lactone **8f** were unsuccessful likely due to the increased sterics of the Lewis base in forming vicinal quaternary centers. Absolute stereochemistry was assigned by comparison of the optical rotation of **8d** with literature values,[23] and was consistent with our previous transition state models of the NCAL toward bicyclic carbocycle fused β-lactones.[41]

Table 3 Catalytic, Asymmetric Synthesis of *N*-Heterocycle-Fused Bicyclic β-Lactones 8 via the NCAL Process



The keto acid **5g** that could deliver a tricyclic-β-lactone was also explored as a substrate for the enantioselective NCAL (Scheme 3). This process could lead to high enantiopurity of tricyclic-β-lactone through a kinetic resolution since the substrate is racemic. Under the optimized conditions, tricyclic β-lactone **8g** was obtained in 65% yield however with only a 70:30 er. Enamine (–)-**17**, derived from presumed *in situ* decarboxylation of the β-lactone adduct, was also isolated in 10% yield, but surprisingly in high enantiopurity (95:5 er).

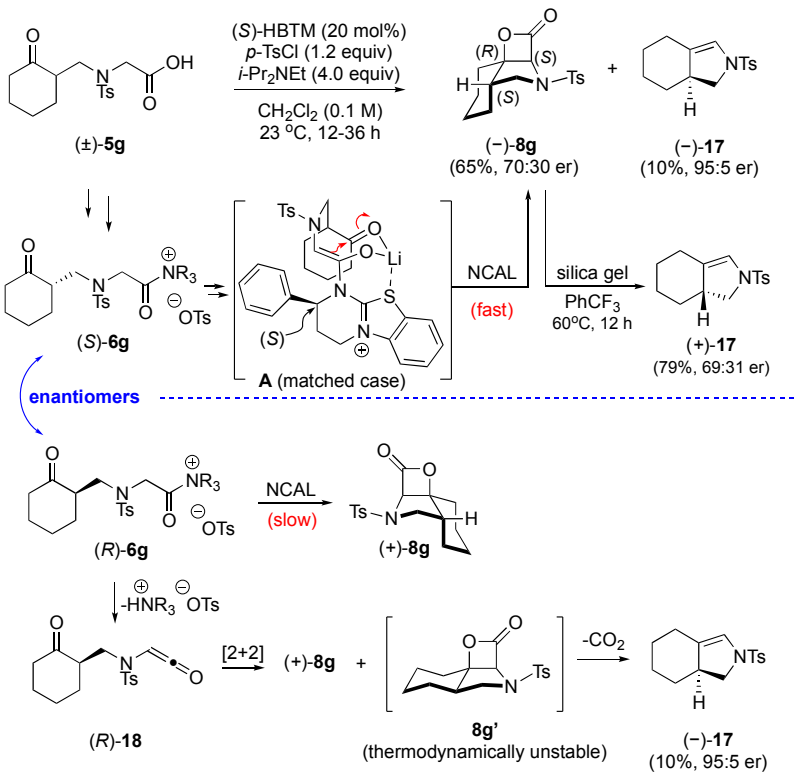
We propose that the observed enantioenriched enamine (–)-**17** is a result of a diastereodivergent process,[42,43] wherein one enantiomeric starting material proceeds through a NCAL pathway ((*S*)-**6g**) while the other ((*R*)-**6g**) proceeds through a [2+2] cycloaddition/decarboxylation pathway (Scheme 3). The NCAL pathway would be expected to lead to high diastereoselectivity and enantioselectivity in the matched case, transition state arrangement **A**, via acylammonium salt (*S*)-**6g**, as observed in the bicyclic series herein and also previously in the carbocyclic series,[9] however an intervening [2+2] cycloaddition pathway with the presumed mismatched case (*i.e.* acylammonium salt (*R*)-**6g**) leads to a non-diastereoselective

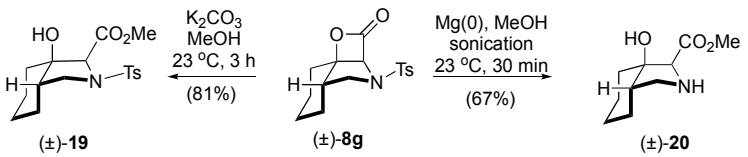
[2+2] cycloaddition pathway providing both diastereomeric β-lactones (+)-**8g** and **8g'**. The presence of the enantiomeric (+)-**8g** serves to lower the enantiopurity of the isolated tricyclic β-lactone (**–**)-**8g** (70:30 er). On the other hand, the strain associated with the diastereomeric β-lactone **8g'**, which could not be isolated likely due to its instability due to strain, leads to *in situ* decarboxylation under the reaction conditions providing enamine (–)-**17** with high enantiopurity since it is derived primarily from ketene (*R*)-**18**. Calculation of the total energy difference between diastereomeric β-lactones **8g** and **8g'** support the hypothesis that β-lactone **8g'** may undergo decarboxylation at ambient temperature ($\Delta E_{\mathbf{8g/8g'}}$ ~2.4-2.6 kcal/mol, from Chem3D and Avogrado using MMFF94 force fields). Heating in the presence of silica gel was required to induce decarboxylation of (+)-**8g**/(**–**)-**8g** and confirmed our prediction that the major product was the enantiomeric enamine (+)-**17** obtained in 79% yield (70:30 er). Overall, while a kinetic resolution is operative in this process, an intervening [2+2] cycloaddition pathway leads to lower

enantiopurity of the tricyclic β-lactone (**–**)-**8g**.

Scheme 3. Enantioselective NCAL leading to tricyclic β-lactone **8g** proceding through transition state arrangement **A** with alkene (–)-**17** as by-product and proposed mechanistic rationale for the high optical purity of alkene (–)-**17**.

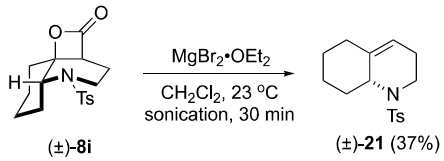
A few transformations of the derived *N*-heterocycle-fused β-lactones were explored. Methanolysis of β-lactone (±)-**8g** under basic conditions afforded hydroxy ester (±)-**19** in 81% yield (Scheme 4). As expected, treatment of β-lactone (±)-**8g** with Mg^{o} in MeOH under sonication conditions led to cleavage of the tosyl group with concomitant opening of the β-lactone to provide amino ester (±)-**20**. Conditions were not found that enabled tosyl deprotection without β-lactone cleavage.





Scheme 4. Transformations of *N*-heterocycle fused tricyclic β-lactone (±)-**8g**

Attempted dyotropic rearrangement of β-lactone (±)-**8i** with stoichiometric amounts of $MgBr_2 \bullet OEt_2$,[9,10,44,45] led to alternative conditions for decarboxylation (37%) providing alkene (±)-**21** albeit in low yield (Scheme 5).



Scheme 5. Decarboxylation of fused tricyclic β-lactone **8i** leading to alkene **21**

In summary, the intramolecular NCAL process has been extended to *N*-linked keto acid substrates leading to the synthesis of pyrrolidine and piperidine-fused β-lactones. Stoichiometric 4-PPY was identified as an optimal Lewis base for the racemic synthesis of several bi- and tricyclic *N*-heterocycle fused β-lactones in moderate to good yields (40-82%) with high diastereoselectivity in all cases (>19:1). Lower yields were obtained when synthesis of a pyrrolidine fused-β-lactone bearing adjacent quaternary carbons was attempted (24%). A catalytic, asymmetric version of these NCAL reactions was optimized and led to moderate to good yields (45-80%) of optically active bicyclic β-lactones (97:3-99:1 er) however lower enantioselectivity was obtained with a tricyclic-β-lactone **8g** (70:30 er). A unique type of diastereodivergent process[42] is proposed to account for an alkene by-product obtained in high enantiomeric purity (95:5 er) through a [2+2] cycloaddition/decarboxylation pathway from racemic starting material. This unique kinetic resolution which delivers two different products

from racemic starting materials is under continued investigation. The described NCAL organocascade allows simultaneous assembly of a nitrogen heterocycle and a fused β-lactone readied for further transformations.

Experimentals

General Information

All non-aqueous reactions were performed under a nitrogen atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2) and Tetrahydrofuran (THF) were dried by passing through activated molecular sieves or alumina (solvent purification system). Diisopropylethylamine (DIPEA) 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. ^{1}H NMR spectra were measured at 600 MHz and 400 MHz and referenced relative to residual chloroform (7.26 ppm) and are reported in parts per million. Coupling constants (*J*) are reported in Hertz (Hz), with multiplicity reported following usual conventions: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; ddq, doublet of doublet of quartets; m, multiplet; bs, broad singlet. ^{13}C NMR spectra were measured at 150 MHz and 101 MHz and referenced relative to residual chloroform (77.23 ppm) and are 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 in the Mass Spectrometry Laboratory (Baylor University) using an ion trap mass analyzer. Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F254 (Silicycle, 250 μm

thickness). Visualization of developed plates was performed by fluorescence quenching. *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.

(*S*)-Homobenzotetramisole (HBTM, **10**)[29] and HBTM-2.1 (**11**)[33] was synthesized according to literature procedures. (*R*)-Benzotetramisole (BTM, **12**) was purchased from TCI chemicals. Alkenes **9a-c**,[22] **9d**,[23] **9g**[27] and **9h**[26] were prepared according to literature procedures.

Representative Procedure for Synthesis of Keto Acid Substrates *via* Sequential Ozonolysis and Pinnick Oxidation as Described for Keto acid 5a: (3-((4-Methyl-*N*-(2-oxopropyl)phenyl)sulfonamido)propanoic acid, 5a): A solution of alkene **9a** (2.70 g, 9.70 mmol, 1.0 equiv) in CH_2Cl_2 was treated with ozone under -78 ºC via gas dispersion tube. After the solution turned pale blue, nitrogen gas was introduced until the blue color faded away. Then, dimethylsulfide (DMS) (14.5 mL, 193.7 mmol, 20.0 equiv) was added at -78 ºC. The reaction mixture was warmed up to 23 ºC and stirred for 18 h. The solution was concentrated *in vacuo,* and the mixture was used directly in the next step without further purification.

The crude aldehyde was dissolved in a mixture of *t*BuOH (60 mL) and water H_2O (20 mL) at 23 ºC. Then, sodium phosphate mono basic (NaH_2PO_4) (10.40 g, 87.3 mmol, 9.0 equiv) and 2-methyl-2-butene (10.50 mL, 97.0 mmol, 10.0 equiv) was added and the reaction mixture was kept stirring until the inorganic salt was completely dissolved. Sodium chlorite (2.67 g, 12.7 mmol, 2.0 equiv), was then added in one portion. Upon completion (as judged by TLC), 1N HCl was added to adjust pH to 2-3. Additional water (100 mL) was added and the aqueous phase was

extracted with ethyl acetate (100 mL×3). The combined organic phase was washed with brine (100 mL) and dried over sodium sulfate. The organic solvent was removed *in vacuo*. The crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford acid **5a** as a white solid (1.95 g, 67%, over 2 steps). TLC (EtOAc, 100%): R_f = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.12 (s, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 2.72 (t, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8, 177.2, 144.1, 136.0, 129.9 (2), 127.6 (2), 58.4, 45.0, 34.4, 27.0, 21.7. IR (thin film): 3200-3600 (br), 1731, 1714 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{13}H_{17}NNaO_5S$ $[M+Na]^+$: 322.0725, found: 322.0725.

4-((4-Methyl-*N*-(2-oxopropyl)phenyl)sulfonamido)butanoic acid (5b): Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation employing alkene **9b** (882 mg, 3.0 mmol, 1.0 equiv) and DMS (4.5 mL, 60.0 mmol, 20.0 equiv) for the ozonolysis and $NaClO_2$ (541 mg, 6.0 mmol, 2.0 equiv), NaH_2PO_4 (3.21 g, 9.0 equiv, 27.0 mmol), 2-methyl-1-butene (3.24 mL, 30.0 mmol, 10.0 equiv), ^{t}BuOH (24 mL), H_2O (8 mL) for the Pinnick oxidation. The crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5b** as a while solid (423 mg, 45% yield over two steps). TLC (EtOAc, 100%): R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 4.00 (s, 2H), 3.24 (t, *J* = 7.1 Hz, 2H), 2.50-2.34 (m, 5H), 2.20 (s, 3H), 4.13 (app p, *J* = 7.1 Hz, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 203.9, 178.0, 144.0, 136.2, 129.9 (2), 127.6 (2), 57.0, 48.4, 30.7, 27.2, 23.1, 21.8; IR (thin film): 2800-3600 (br), 1730, 1650 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{14}H_{19}NO_5SNa$ $[M+Na]^+$: 336.0882, found: 336.0878.

5-((4-Methyl-*N*-(2-oxopropyl)phenyl)sulfonamido)pen-tanoic acid (5c): Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation employing alkene.

9c (982 mg, 3.2 mmol, 1.0 equiv), DMS (4.8 mL, 20.0 equiv, 64.0 mmol) were used for ozonolysis. $NaClO_2$ (865 mg, 9.6 mmol, 3.0 equiv), NaH_2PO_4 (3.45 g, 29.0 mmol, 9.0 equiv), 2-methyl-1-butene (3.45 mL, 32.0 mmol, 10.0 equiv), ^{t}BuOH (24 mL), H_2O (8 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5c** as a colorless oil (579 mg, 56% yield over two steps). TLC (EtOAc, 100%): R_f= 0.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 3.93 (s, 2H), 3.15 (t, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.19 (s, 3H), 1.74 – 1.33 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4, 178.9, 143.9, 136.1, 129.9 (2), 127.6 (2), 57.0, 48.9, 33.4, 27.5, 27.2, 21.8, 21.7; IR (thin film): 1732 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{15}H_{21}NO_5SNa$ $[M+Na]^+$: 350.1038, found: 350.1028.

***N*-(3-oxobutyl)-*N*-tosylglycine (5d)**: Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation employing alkene **9d**[23] (1.20 g, 4.27 mmol, 1.0 equiv), DMS (3.2 mL, 42.7 mmol, 10.0 equiv) were used for ozonolysis. $NaClO_2$ (1.15 g, 12.7 mmol, 3.0 equiv), NaH_2PO_4 (4.60 g, 38.6 mmol, 9.0 equiv), 2-methyl-1-butene (4.60 mL, 42.7 mmol, 10.0 equiv), ^{t}BuOH (30 mL), H_2O (10 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5d** as a white solid (817 mg, 64% yield over two steps). TLC (EtOAc, 100%): R_f= 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.10 (s, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.90 (t, *J* = 6.4 Hz, 2H), 2.43 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8, 174.2, 144.1, 136.1, 130.0 (2), 127.5 (2), 50.5, 44.3, 43.9, 30.3, 21.8.; IR (thin film): 3000-3700, 1639; HRMS (ESI+) *m/z* calcd for $C_{13}H_{17}NNaO_5S$ $[M+Na]^+$: 322.0725, found: 322.0724.

***N*-(3-oxobutyl)-*N*-tosylglycine (5e)**: To a solution of amino ester **9e** (1.13g, 3.6 mmol, 1.2 equiv), 5-hydroxy-2-pentanone (306 mg, 3.0 mmol, 1.0 equiv) and triphenylphosphine (786 mg, 3.0 mmol, 1.0 equiv) in THF (30 mL) was added diethyl azodicarboxylate in toluene (1.56 mL, 3.6 mmol, 1.2 equiv) at 0 ºC dropwise over 5 min. Upon completion (as judged by TLC), the solvent was removed by rotary evaporation. The crude product was purified by automated flash chromatography (0 → 50%, EtOAc/hexanes) to afford keto ester **5e** inseparable from hydrazine derived from diethyl azodicarboxylate. The crude mixture (1.05 g) was taken directly into the next step without further purification.

To a solution of the crude keto ester in methanol was added Pd/C (105 mg). The suspension was charged with H_2 and stirred under H_2 atmosphere at 23 ºC. Upon completion (as judged by TLC), the suspension was filtered through a pad of Celite and the solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5e** as a white solid (508 mg, 52% yield). TLC (EtOAc): R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.69 (br, 1H), 3.98 (s, 2H), 3.20 (t, *J* = 6.7 Hz, 2H), 2.57 (t, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 2.14 (s, 3H), 1.76 (app p, *J* = 6.7, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 173.5, 143.9, 136.3, 129.9(2), 127.5(2), 48.5, 48.3, 39.9, 30.3, 21.7, 21.6; IR (thin film): 2800-3600 (br), 1715 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{14}H_{19}NO_5SNa$ $[M+Na]^+$: 336.0882, found: 336.0873.

Benzyl 2-methyl-3-((4-methyl-*N*-(2-oxopropyl)phenyl)sulf-onami-do)propanoate (S1): To a solution of allylic amine **9f** (1.00 g, 1.0 equiv, 4.4 mmol) and K_2CO_3 (1.84 g, 3.0 equiv, 13.2 mmol) in acetonitrile at 23 ºC was added benzyl methacrylate (1.56 g, 2.0 equiv, 8.9 mmol). The reaction mixture was stirred at 23 ºC for 12 h. Upon completion (as judged by TLC), the solid was removed by filtration and the organic solvent was removed by rotary evaporation. The crude

product was then purified by automated flash chromatography (0 → 50%, EtOAc/hexanes) to afford ester **S1** as a colorless oil (1.28 g, 72% yield). TLC (EtOAc/Hexanes, 1:1 v/v): R_f = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.29 (m, 5H), 7.27 (d, *J* = 8.2 Hz, 2H), 5.09 (d, *J* = 19.5 Hz, 1H), 5.07 (d, *J* = 19.5 Hz, 1H), 4.85 (d, *J* = 17.7 Hz, 1H), 3.67 (d, *J* = 24.2 Hz, 1H), 3.64 (d, *J* = 24.2 Hz, 1H), 3.33 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.33 (dd, J = 56.0, 14.4, 7.1 Hz, 1H), 3.19 (dd, J = 56.0, 14.4, 7.1 Hz, 1H), 2.89 (td, 7.1, 7.1 Hz, 1H), 2.41 (s, 3H), 1.65 (s, 3H), 1.17 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 143.5, 140.8, 136.6, 136.0, 129.8 (2), 128.7 (2), 128.4, 128.3 (2), 127.5 (2), 115.0, 66.6, 56.2, 51.3, 39.5, 21.7, 20.1, 15.6; IR (thin film): 1733, 1160 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{27}NO_4SNa$ $[M+Na]^+$: 424.1558 found: 424.1578.

2-Methyl-3-((4-methyl-*N*-(2-oxopropyl)phenyl)sulfonamido) propanoic acid (5f): A solution of alkene ester **S1** (1.20 g, 1.0 equiv, 3.0 mmol) in CH_2Cl_2 (60 mL) under -78 ºC was treated with ozone. After the solution turned pale blue, nitrogen gas was introduced until the blue color faded away. Then, DMS (2.3 mL, 30 mmol, 10.0 equiv) was added at -78 ºC. The reaction mixture was warmed up to 23 ºC and stirred overnight. The solvent was removed by rotary evaporation and the crude keto ester was directly used for the next step without further purifications.

To a solution of the crude keto ester in methanol (60 mL) was added Pd/C (122 mg, 10% wt). The suspension was charged with H_2 and stirred under H_2 atmosphere at 23 ºC. Upon completion (as judged by TLC), the suspension was filtered through a pad of Celite and the solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5f** as a white solid (695 mg, 74% yield over two steps). TLC (EtOAc*)*: R_f= 0.38; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.10 (d, *J* = 2.1Hz , 2H), 3.31 (d, *J* = 7.1 Hz, 2H), 2.87 (td,

J = 7.1, 7.1 Hz, 1H), 2.42 (s, 3H), 2.12 (s, 3H), 1.20 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.8, 180.7, 144.0, 136.0, 129.9 (2), 127.7 (2), 58.6, 52.0, 40.1, 27.0, 21.8, 15.5; IR (thin film): 1732 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{14}H_{19}NO_5SNa$ $[M+Na]^+$: 336.0882, found: 336.0897.

***N*-((2-oxocyclohexyl)methyl)-*N*-tosylglycine (5g):** To a solution of amino ketone **9g**[27] (1.50 g, 5.0 mmol, 1.0 equiv) and K_2CO_3 (2.10 g, 15 mmol, 3.0 equiv) in DMF (25 mL) was added benzyl 2-bromoacetate (2.3 mL, 10.0 mmol, 2.0 equiv). The reaction was stirred for 3 h at ambient temperature (23 ºC). Upon completion (as judged by TLC), the inorganic salts were removed through filtration. Diethyl ether (100 mL) was added, and the organic phase was washed with water (100 mL x 2) and brine (100 mL). The organic phase was dried over $MgSO_4$. The solvent was removed by rotary evaporation. The crude mixture was filtered through a short pad of silica gel (100% hexane, then 100% EtOAc) to remove the excess benzyl 2-bromoacetate. The crude mixture was directly used in the next step without further purification.

To a solution of the crude keto ester (1.25 g) in methanol was added Pd/C (125 mg, 10 wt%). The suspension was charged with H_2 and stirred under H_2 atmosphere at 23 ºC for 4 h. Upon completion (as judge by TLC), the suspension was filtered through a pad of Celite and the solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5g** as a white solid (864 mg, 51% yield). (EtOAc, 100%): R_f = 0.60; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.23 (d, *J* = 18.5 Hz, 1H), 4.04 (d, *J* = 18.5 Hz, 1H), 3.40 (d, *J* = 15.0 Hz, 1H), 3.23 (d, *J* = 15.0 Hz, 1H), 2.82 (td, *J* = 12.5, 6.0 Hz, 1H), 2.43 (s, 3H), 2.37 (dddd, *J* = 13.4, 4.6, 3.1, 1.5 Hz, 1H), 2.31 (dt, *J* = 13.1, 6.1 Hz, 1H), 2.25 (ddd, *J* = 13.2, 5.7, 2.9 Hz, 1H), 2.09 (ddt, *J* = 12.5, 6.1, 2.9 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.77 – 1.54 (m, 2H), 1.37 (dq, *J* =

12.8, 3.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 213.1, 174.4, 144.0, 136.2, 129.9 (2), 127.5 (2), 51.7, 50.5, 49.4, 42.3, 32.6, 28.2, 25.2, 21.7; IR (thin film): 1704 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{16}H_{21}NNaO_5S$ $[M+Na]^+$: 362.1038, found: 362.1034.

Representative Procedure for the Sequential *N*-alkylation and 2-iodoxybenzoic acid (IBX) Oxidation as Described for S2. *N*-(but-3-en-1-yl)-4-methyl-*N*-(2-oxocyclohexyl)benzenesulfon-amide (S2): To a solution of amino alcohol **9h**[26] (3.23 g, 10.0 mmol 1.0 equiv) and K_2CO_3 (5.2 g, 30.0 mmol, 3.0 equiv) in acetone (50 mL) was added 4-bromo-1-butene (2.8 mL, 20.0 mmol, 2.0 equiv) at 23 ºC. The reaction mixture was heated up to 65 ºC for 24 h. Upon completion (as judged by TLC), the inorganic salts were removed by filtration and the solvent was removed by rotary evaporation. The remaining 4-bromo-1-butene was removed under high vacuum. The crude product was directly used in the next step without further purification.

To a solution of crude secondary alcohol in ethyl acetate (50 mL) was added IBX. The reaction mixture was heated up to 80 ºC for 12 h. Upon completion (as judged by TLC), the solid was removed by filtration and the solvent was removed by rotary evaporation. The crude product was purified by automated flash chromatography (0 → 50%, EtOAc/hexanes) to afford keto alkene **S2** (1.48 g, 46% yield over two steps). TLC (EtOAc:Hexanes, 1:3, v/v): R_f= 0.43; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.70 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.09 – 4.85 (m, 2H), 4.57 (dd, *J* = 12.2, 5.7 Hz, 1H), 3.39 (ddd, *J* = 15.5, 11.0, 5.0 Hz, 1H), 2.92 (ddd, *J* = 15.5, 11.0, 5.5 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.43 – 2.35 (m, 4H), 2.34 – 2.17 (m, 3H), 2.14 – 1.94 (m, 2H), 1.90 – 1.68 (m, 2H), 1.63 – 1.48 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.0, 143.3, 137.4, 135.2, 129.6 (2), 127.5 (2), 116.8, 66.2, 46.3, 42.0, 36.2, 34.3,

26.8, 25.3, 21.8; IR (thin film): 1720 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{17}H_{23}NO_3SNa$ $[M+Na]^+$: 344.1296, found: 344.1291.

4-Methyl-*N*-(2-oxocyclohexyl)-*N*-(pent-4-en-1-yl)benzenesulfonamide (S3): Prepared according to the representative procedure for sequential *N*-alkylation and IBX oxidation. Amino alcohol **9h** (5.38 g, 20.0 mmol, 1.0 equiv), K_2CO_3 (10.3 g, 60.0 mmol), acetone (100 mL), and 5-bromo-1-pentene (6.0 mL, 40.0 mmol, 2.0 equiv) were used for *N*-alkylation. 2-iodoxybenzoic acid (IBX) (10.2 g, 40 mmol, 2.0 equiv) and ethyl acetate (100 mL) were used for IBX oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 50%, EtOAc/hexanes) to afford keto alkene **S3** (3.87 g, 57% yield over two steps). TLC (EtOAc:Hexanes, 1:3, v/v): R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.75 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.19 – 4.87 (m, 2H), 4.56 (dd, *J* = 12.2, 5.7 Hz, 1H), 3.32 (ddd, *J* = 15.4, 11.3, 4.4 Hz, 1H), 2.86 (ddd, *J* = 15.7, 10.8, 5.3 Hz, 1H), 2.49 – 2.34 (m, 4H), 2.34-2.18 (m, 2H) 2.09 – 1.88 (m, 5H), 1.86 – 1.67 (m, 2H), 1.67 – 1.46 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.0, 143.3, 137.8, 137.5, 129.6 (2), 127.5 (2), 115.4, 66.1, 46.4, 42.0, 34.3, 31.3, 30.9, 26.8, 25.4, 21.8; IR (thin film): cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{18}H_{25}NO_3SNa$ $[M+Na]^+$: 358.1453, found: 358.1450.

***N*-(3-oxobutyl)-*N*-tosylglycine (5h)**: Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation. Keto alkene **S2** (605 mg, 1.0 equiv, 1.8 mmol) and DMS (1.4 mL, 10.0 equiv, 18.0 mmol) was used for ozonolysis. $NaClO_2$ (0.38 g, 2.0 equiv, 3.6 mmol), NaH_2PO_4 (1.10 g, 5.0 equiv, 38.6 mmol), 2-methyl-2-butene (2.0 mL, 10.0 equiv, 18.0 mmol), *t*-BuOH (14 mL), H_2O (4.5 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5h** as a white solid (817 mg, 46% yield over two steps). TLC

(EtOAc, 100%): R_f= 0.62; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 4.59 (dd, *J* = 12.4, 5.7 Hz, 1H), 3.54 (ddd, J = 15.5, 10.0, 5.5 1H), 3.26 (ddd, *J* = 15.5, 10.0, 5.5 Hz, 1H), 3.04 (ddd, *J* = 17.0, 9.9, 5.5 Hz, 1H), 2.70 (ddd, *J* = 17.0, 10.0, 5.5 Hz, 1H), 2.41 (m, 4H), 2.31 – 2.16 (m, 2H), 2.11 – 1.94 (m, 1H), 1.92 – 1.69 (m, 2H), 1.56 (qt, *J* = 12.9, 3.8 Hz, 1H), 1.23 (dt, *J* = 20.1, 7.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.0, 176.6, 143.7, 136.8, 129.8 (2), 127.5 (2), 66.5, 41.9, 41.6, 36.2, 33.6, 26.7, 25.2, 21.8; IR (thin film):1720 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{16}H_{21}NNaO_5S$ $[M+Na]^+$: 362.1038, found: 362.1034.

***N*-(3-oxobutyl)-*N*-tosylglycine (5i)**: Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation. **S3** (1.20 g, 1.0 equiv, 3.60 mmol), DMS (2.7 mL, 10 equiv, 36.0 mmol) were used for ozonolysis. $NaClO_2$ (975 mg, 3.0 equiv, 10.8 mmol), NaH_2PO_4 (2.20 g, 5.0 equiv, 18.0 mmol), 2-methyl-2-butene (4.0 mL, 10.0 equiv, 36.0 mmol), *t*-BuOH (25 mL), H_2O (8 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford ketoacid **5i** as a white solid (726 mg, 65% yield over two steps). TLC (EtOAc, 100%): R_f= 0.65; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 4.55 (dd, *J* = 12.7, 5.7 Hz, 1H), 3.34 (ddd, *J* = 15.5, 10.2, 5.4 Hz, 1H), 2.98 (ddd, *J* = 15.5, 10.2, 5.4 Hz, 1H), 2.45 – 2.33 (m, 6H), 2.31 – 2.18 (m, 2H), 2.14 – 1.95 (m, 3H), 1.95 – 1.68 (m, 3H), 1.55 (dddd, *J* = 17.7, 13.9, 8.9, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.1, 178.8, 143.5, 137.1, 129.6 (2), 127.5 (2), 66.1, 45.8, 42.0, 34.0, 31.1, 26.8, 26.4, 25.3, 21.8; IR (thin film):1722 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{17}H_{23}NNaO_5S$ $[M+Na]^+$: 376.1195, found: 376.1189.

Representative Procedure for the Racemic Nucleophile-Catalyzed Aldol Lactonization (NCAL) Cascade as Described for β-Lactone (±)-8a. 5-Methyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one ((±)-8a): To an oven-dried, round-bottom flask equipped with a magnetic stir bar was added *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol, 1.5 equiv), 4-PPY (22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL) and *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) under nitrogen atmosphere at 23°C. The keto acid **5a** (30 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise through syringe pump over 3 h. After the addition was complete, the reaction was allowed to stir for an additional 9 h. Upon completion (as judged by TLC), the solvent was concentrated by rotary evaporation and the crude mixture was purified by flash chromatography (0 → 40%, EtOAc/hexanes) to afford the β-lactone (±)-**8a** as a white solid (21 mg, 72% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.34. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 3.94 (d, *J* = 10.7 Hz, 1H), 3.88 (d, *J* = 11.9 Hz, 1H), 3.59 (d, *J* = 6.2 Hz, 1H), 2.97 (dd, *J* = 10.7, 6.4 Hz, 1H), 2.75 (d, *J* = 11.9 Hz, 1H), 2.45 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 167.2, 144.7, 132.6, 130.1 (2), 128.1 (2), 83.7, 58.8, 55.4, 48.1, 21.81, 19.4; IR (thin film): 1826 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{13}H_{15}NO_4SNa$ $[M+Na]^+$: 304.0619, found: 304.0622.

1-Methyl-3-tosyl-8-oxa-3-azabicyclo[4.2.0]octan-7-one ((±)-8b): Prepared according to representative procedure for the racemic NCAL using *p*-toluenesulfonyl chloride (p-TsCl, 28 mg, 0.15 mmol, 1.5 equiv), 4-pyrrolidinopyridine (4-PPY, 22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL), *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) and keto acid **5b** (31 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0 → 40%, EtOAc/hexanes) to afford β-lactone (±)-**8b** as a white solid (12 mg, 42% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.3 Hz, 1H),

7.33 (d, *J* = 8.3 Hz, 2H), 3.85 (d, *J* = 14.4 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.27 (d, *J* = 14.4), 3.22 (td, *J* = 11.8, 6.0 Hz, 1H), 2.43 (s, 3H), 2.18 – 2.07 (m, 1H), 1.93 (ddt, *J* = 14.9, 10.6, 6.4 Hz, 1H), 1.59 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 144.2, 134.4, 130.0 (2), 127.7 (2), 76.5, 51.8, 49.8, 40.8, 23.2, 21.8, 19.7; IR (thin film): 1812 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{14}H_{17}NO_4SNa$ $[M+H]^+$: 318.0776, found: 318.0784.

5-methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.0]heptan-7-one ((±)-8d): Prepared according to representative procedure for the racemic NCAL using *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol, 1.5 equiv), 4-PPY (22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL) and *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) under nitrogen atmosphere at 23°C and keto acid **5d** (30 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (±)-**8d** as a white solid (22 mg, 78% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.07 (s, 1H), 3.99 (dd, J = 11.2, 8.2 Hz, 1H), 3.14 (td, *J* = 11.4, 5.8 Hz, 1H), 2.43 (s, 3H), 2.21 (dd, *J* = 14.3, 5.8 Hz, 1H), 1.80 (ddd, *J* = 14.3, 11.6, 8.2 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 164.7, 144.7, 135.0, 130.0 (2), 128.1 (2), 87.5, 73.7, 46.9, 35.4, 21.8, 20.9; IR (thin film): 1829 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{13}H_{15}NO_4SNa$ [M+Na]+: 304.0619, found: 304.0633.

6-methyl-2-tosyl-7-oxa-2-azabicyclo[4.2.0]octan-8-one ((±)-8e): Prepared according to representative procedure for the racemic NCAL using *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol, 1.5 equiv), 4-PPY (22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL), *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) and keto acid **5e** (31 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (±)-**8e** as a white solid (14 mg, 48% yield). TLC

(EtOAc:hexanes, 3:7 *v/v*): R_f = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.20 (s, 1H), 3.49 (dt, *J* = 11.1, 8.9 Hz, 1H), 3.28 – 3.07 (m, 1H), 2.43 (s, 3H), 2.19 – 2.09 (m, 1H), 1.78 (m, 3H), 1.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 144.4, 135.2, 130.0 (2), 127.8 (2), 80.9, 65.1, 42.0, 31.1, 24.5, 21.8, 16.8; IR (thin film): 1828 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{14}H_{17}NO_4SNa$ $[M+Na]^+$: 318.0776, found: 318.0784.

1,5-Dimethyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one ((±)-8f): Prepared according to representative procedure for the racemic NCAL using *p*-toluenesulfonyl chloride (56 mg, 0.30 mmol, 1.5 equiv), 4-PPY (44 mg, 0.30 mmol, 1.5 equiv), CH_2Cl_2 (3.0 mL), *N*,*N*-diisopropylethylamine (73.0 μL, 0.50 mmol, 2.5 equiv) and keto acid **5f** (62 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (±)-**8f** as a white solid (14 mg, 24% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.46; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.95 (d, *J* = 10.6 Hz, 1H), 3.91 (d, *J* = 11.9 Hz, 1H), 2.78 (d, *J* = 11.9, 1H), 2.65 (d, *J* = 10.6, 1H), 2.45 (s, 3H), 1.50 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 144.6, 132.9, 130.1 (2), 128.1 (2), 86.1, 62.8, 55.7, 54.2, 21.8, 16.4, 11.4; IR (thin film): 1826 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{14}H_{17}NO_4SNa$ $[M+Na]^+$: 318.0776, found: 318.0771.

3-tosyloctahydro-2H-oxeto[3,2-c]isoindol-2-one ((±)-8g): Prepared according to the representative procedure for the racemic NCAL as described for (±)-**8a** using *p*-toluenesulfonyl chloride (85 mg, 0.45 mmol, 1.5 equiv), 4-PPY (66 mg, 0.45 mmol, 1.5 equiv), CH_2Cl_2 (5.5 mL), *N*,*N*-diisopropylethylamine (0.12 mL, 0.75 mmol, 2.5 equiv) and keto acid **5g** (101 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone **(±)-8g** as a white solid (76 mg, 79% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H),

7.31 (d, *J* = 8.3 Hz, 2H), 5.02 (s, 1H), 3.57 (d, *J* = 10.1 Hz, 1H), 3.24 (dd, *J* = 10.1, 5.0 Hz, 1H), 2.42 (s, 3H), 2.25 (ddd, *J* = 11.9, 6.4, 4.9 Hz, 1H), 2.21 – 2.14 (m, 1H), 2.02 – 1.84 (m, 3H), 1.72 (ddd, *J* = 17.4, 10.2, 6.6 Hz, 1H), 1.39 (app dq, *J* = 13.6, 3.7 Hz, 1H), 1.32 – 1.15 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2, 144.3, 135.5, 129.8 (2), 128.0 (2), 89.0, 71.4, 52.0, 41.0, 30.3, 28.6, 23.7, 23.5, 21.8; IR (thin film): 1829 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{16}H_{19}NO_4SNa$ $[M+Na]^+$: 344.0932, found: 344.0938.

4-tosyloctahydro-2H-oxeto[3,2-c]indol-2-one ((±)-8h): Prepared according to the representative procedure for the racemic NCAL using *p*-toluenesulfonyl chloride (85 mg, 0.45 mmol, 1.5 equiv), 4-PPY (66 mg, 0.45 mmol, 1.5 equiv), CH_2Cl_2 (5.5 mL), *N*,*N*-diisopropylethylamine (0.12 mL, 0.75 mmol, 2.5 equiv) and keto acid **5h** (101 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone **(±)-8h** as a white solid (79 mg, 82% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.07 (dd, *J* = 10.8, 7.0 Hz, 1H), 3.85 (d, *J* = 12.0 Hz, 1H), 3.58 (dd, *J* = 12.0, 6.5 Hz, 1H), 3.50 (d, *J* = 6.5 Hz, 1H), 2.42 (s, 3H), 2.32 (app qt, *J* = 7.1, 2.4 Hz, 1H), 2.28 – 2.14 (m, 1H), 1.97 (td, *J* = 13.7, 4.8 Hz, 1H), 1.88 (ddt, *J* = 13.5, 4.9, 2.6 Hz, 1H), 1.76 (dt, *J* = 8.9, 2.7 Hz, 1H), 1.33 – 1.24 (m, 2H), 1.24 – 1.10 (m, 1H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 167.8, 144.1, 136.7, 129.9 (2), 127.4 (2), 86.3, 61.5, 57.6, 45.7, 31.1, 29.3, 23.6, 22.8, 21.8; IR (thin film): 1834 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{16}H_{19}NO_4SNa$ $[M+Na]^+$: 344.0932, found: 344.0929.

5-tosyloctahydrooxeto[3,2-d]quinolin-2(2aH)-one ((±)-8i): Prepared according to the representative procedure for the racemic NCAL using *p*-toluenesulfonyl chloride (85 mg, 0.45 mmol, 1.5 equiv), 4-PPY (66 mg, 0.45 mmol, 1.5 equiv), CH_2Cl_2 (5.5 mL), *N*,*N*-diisopropylethylamine (0.12 mL, 0.75 mmol, 2.5 equiv)and keto acid **5i** (106 mg, 0.30 mmol, 1.0

equiv) in CH_2Cl_2 (0.5 mL) . The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone **(±)-8i** as a white solid (69 mg, 69% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.54; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.02 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.70 (ddd, *J* = 11.5, 6.1, 2.1 Hz, 1H), 3.28 (dd, *J* = 4.7, 2.8 Hz, 1H), 3.06 (td, *J* = 12.1, 5.9 Hz, 1H), 2.41 (s, 3H), 2.34 (ddd, *J* = 12.8, 5.3, 2.4 Hz, 1H), 2.27 – 2.16 (m, 1H), 2.16 – 2.06 (m, 1H), 1.97 (dd, *J* = 12.4, 3.1 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.77 (dt, *J* = 13.1, 2.9 Hz, 1H), 1.49 (ddd, *J* = 12.7, 12.2, 3.3 Hz, 1H), 1.45 – 1.30 (m, 1H), 1.23 – 1.05 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 143.8, 135.1, 129.7 (2), 127.6 (2), 78.9, 56.3, 50.5, 38.9, 36.8, 35.3, 24.4, 23.9, 21.8, 19.5; IR (thin film): 1823 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{17}H_{21}NO_4SNa$ $[M+Na]^+$: 358.1089, found: 358.1084.

Representative Procedure for the Enantioselective NCAL as Described for β-Lactone (–)-8a. (1S,5S)-5-Methyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one ((–)-8a): To an oven-dried, 10 mL round-bottomed flask equipped with a magnetic stir bar was added *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.25 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL) and *N*,*N*-diisopropylethylamine (0.18 mL, 1.0 mmol, 4.0 equiv). To this mixture was added keto acid **5a** (80.5 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) through syringe pump over 6 h. After the addition was complete, the reaction was allowed to stir for an additional 6 h. Upon completion (as judged by TLC), the reaction mixture was diluted with ether (20 mL), and the organic phase was then washed with water (2×20 mL) to remove H nig's base and then brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated by rotary evaporation. The crude mixture was purified by normal flash chromatography (0 → 40%, EtOAc/hexanes) to afford the β-lactone (–)-**8a** as a white solid (55 mg, 78% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.34; $[\alpha]_D^{20}$ -6.00

(c = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 19.6 min, t_{minor} = 24.9 min; 99:1 er. Absolute stereochemistry was assigned by analogy to β-lactone (–)-**8d** given that (*S*)-HBTM was employed as Lewis base.

(1S,6S)-1-Methyl-3-tosyl-8-oxa-3-azabicyclo[4.2.0]octan-7-one ((–)-8b): Prepared according to representative procedure for the enantioselective NCAL using *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.25 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5b** (79 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 ml). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (–)-**8b** as a white solid (33 mg, 45% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.40; $[\alpha]_D^{20}$ –78.40 (c = 0.5, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 17.5min, t_{major} = 21.0 min; 99:1 er. Absolute stereochemistry was assigned by analogy to β-lactone (–)-**8d** given that (*S*)-HBTM was employed as Lewis base.

(1S,5R)-5-Methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.0]heptan-7-one ((–)-8d): Prepared according to representative procedure for the enantioselective NCALusing *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.3 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5d** (75 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (–)-**8d** as a white solid (56 mg, 80% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.37; $[\alpha]_D^{20}$ = -119.20 (c = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic

racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 16.1 min, t_{minor} = 20.6 min; 97:3 er. Absolute stereochemistry was assigned by comparison of the optical rotation to a literature value: $[\alpha]_D^{25}$ -127 (*c* = 1.08, $CHCl_3$).[23]

(1*S*,6*R*)-6-methyl-2-tosyl-7-oxa-2-azabicyclo[4.2.0]octan-8-one ((+)-8e): Prepared according to representative procedure for the enantioselective NCAL using *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.3 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5e** (79 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2. The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (+)-**8e** as a white solid (38 mg, 48% yield). TLC (EtOAc:hexanes, 1:1 *v/v*): R_f = 0.45; $[\alpha]_D^{20}$ +45.60 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 11.0 min, t_{major} = 13.3 min; 99:1 *er*. Absolute stereochemistry was assigned by analogy to β-lactone (–)-**8d** given that (*S*)-HBTM was employed as Lewis base.

(2a*S*,4a*S*,8a*R*)-3-tosyloctahydro-2H-oxeto[3,2-c]isoindol-2-one ((–)-8g): Prepared according to representative procedure for the enantioselective NCAL using *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.3 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5g** (85 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (–)-**8g** (55 mg, 65% yield) as a white solid. TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.52; $[\alpha]_D^{20}$ -51.20 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ =

230 nm: t_{major} = 21.2 min, t_{minor} = 25.0 min; 71:29 er. Absolute stereochemistry of the major enantiomer was assigned by analogy to tricyclic carbocycle fused-β-lactones obtained previously given that (*S*)-HBTM was employed as Lewis base (*cf.* Scheme 3).[9]

(*S*)-2-tosyl-2,4,5,6,7,7a-hexahydro-1H-isoindole ((*S*)-17): Enamine (*S*)-**17** was obtained as a side product from the synthesis of (–)-**8g** and was obtained as a white solid (7 mg, 10% yield). TLC (EtOAc:hexanes, 1:4 *v/v*): R*f* = 0.55; $[\alpha]_D^{20}$ -8.00 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.01 (t, *J* = 2.0 Hz, 1H), 3.68 (dd, *J* = 10.9, 10.0 Hz, 1H), 3.01 (dd, *J* = 10.9, 7.2 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.43 (s, 3H), 2.41 – 2.26 (m, 2H), 1.90 – 1.70 (m, 1H), 1.71 – 1.61 (m, 1H), 1.31 – 1.02 (m, 3H), 0.77 (dq, *J* = 12.4, 3.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.7, 133.1, 129.8, 129.7 (2), 128.0 (2), 121.09, 53.8, 43.2, 34.4, 27.3, 25.7, 25.3, 21.8; IR (thin film): 1597 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{15}H_{19}NO_2SNa$ $[M+Na]^+$: 300.1034, found: 300.1030. Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 9.6 min, t_{minor} = 11.9 min; Enantiomeric ratio = 95:5.

(*R*)-2-tosyl-2,4,5,6,7,7a-hexahydro-1H-isoindole ((*R*)-17): To a solution of (–)-**8g** (16 mg, 0.05 mmol, 1.0 equiv) in $PhCF_3$ (0.5 mL) was added silica gel (160 mg). The reaction mixture was heated to 60 ˚C for 12 h. Upon completion (as judged by TLC), the crude mixture was purified by flash chromatography (0→20%, EtOAc/hexanes) to afford (*R*)-**17** as a white solid (11 mg, 79% yield). NMR data matched that obtained for (*S*)-**17** (*vide infra*). $[\alpha]_D^{20}$ +2.12 (*c* = 1.0, $CHCl_3$); Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 230

nm: t_{major} = 9.7 min, t_{minor} = 12.0 min; 69:31 er.

Methyl-7a-hydroxy-2-tosyloctahydro-1H-isoindole-1-carboxy-late ((±)-19): To a solution of **8g** (33 mg, 0.10 mmol, 1 equiv) in methanol (1.0 mL) was added K_2CO_3 (18 mg, 0.13 mmol, 1.3 equiv). The reaction mixture was stirred at 23 ºC for 3 h. Upon completion (as judged by TLC), the inorganic salts were removed through filtration. The solvent was removed by rotary evaporation. The crude product was then purified by flash chromatography (0 → 30%, EtOAc/hexanes) to afford hydroxy ester (±)-**19** as a white solid (29 mg, 82% yield). TLC (EtOAc:hexanes, 1:3 *v/v*): R_f = 0.65; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.17 (s, 1H), 3.73 (s, 3H), 3.59 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.18 (dd, *J* = 9.6, 6.2 Hz, 1H), 2.43 (s, 3H), 2.31 (brs, 1H), 2.25 (td, *J* = 6.5, 6.5 Hz, 1H), 1.65 – 1.43 (m, 4H), 1.41 – 1.27 (m, 3H), 1.09 (ddd, *J* = 14.6, 11.7, 6.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 143.9, 135.5, 129.8 (2), 127.7 (2), 79.3, 67.3, 52.6, 50.5, 43.6, 33.5, 24.6, 22.2, 22.2, 21.8; IR (thin film): 3491, 1742 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{17}H_{23}NNaO_5S$ $[M+Na]^+$: 376.1195, found: 376.1191.

Methyl 7a-hydroxyoctahydro-1H-isoindole-1-carboxylate ((±)-20): To a solution of (±)-**8g** (33 mg, 0.10 mmol, 1 equiv) in methanol (2.0 mL) under nitrogen atmosphere was added magnesium powder (48 mg, 2.0 mmol, 20 equiv). The reaction mixture was sonicated at 23 ºC for 30 min. Upon completion (as judged by TLC), the crude product was directly purified by flash chromatography (9:90:1, MeOH: CH_2Cl_2: NEt_3) to afford amino hydroxy ester (±)-**20** as a white solid (13 mg, 67% yield). TLC (MeOH: CH_2Cl_2: NEt_3, 10:90:4 *v/v*): R_f = 0.55; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (s, 1H), 3.77 (s, 3H), 3.47 (dd, *J* = 10.3, 5.5 Hz, 1H), 2.71 (dd, *J* = 9.8, 2.1 Hz, 1H), 2.55 (brs, 1H), 2.24 (dt, *J* = 13.5, 3.7 Hz, 2H), 1.93 (dtd, *J* = 11.1, 5.9, 2.1 Hz, 1H), 1.79 – 1.70 (m, 2H), 1.69 – 1.63 (m, 1H), 1.56 (ddd, *J* = 13.5, 12.2, 4.4 Hz, 1H), 1.44 – 1.32 (m,

1H), 1.33 – 1.21 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 173.1, 81.4, 64.8, 52.4, 50.6, 47.5, 33.5, 29.2, 24.5, 23.4; IR (thin film): 3100-3700 (br), 1738 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{10}H_{18}NO_3$ $[M+H]^+$: 220.1287, found: 220.1301.

1-tosyl-1,2,3,5,6,7,8,8a-octahydroquinoline ((±)-21): To a solution of tricyclic β-lactone (±)-**8i** (33 mg, 0.10 mmol, 1 equiv) in CH_2Cl_2 (1.0 mL) under nitrogen atmosphere was added magnesium bromide etherate (28 mg, 0.11 mmol, 1.1 equiv). The reaction mixture was sonicated at 23 ºC for 30 min. Upon completion (as judged by TLC), the crude product was directly purified by flash chromatography (0 - 25% EtOAc/Hexanes) to afford alkene (±)-**21** as a colorless liquid (13 mg, 37% yield). TLC (EtOAc:hexanes, 1:2 *v/v*): R_f = 0.80; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.37 – 5.31 (m, 1H), 4.10 (d, *J* = 6.9 Hz, 1H), 3.93 – 3.59 (m, 1H), 3.04 (ddd, *J* = 13.9, 11.5, 4.1 Hz, 1H), 2.40 (s, 3H), 2.22 (ddt, *J* = 13.0, 4.3, 2.3 Hz, 1H), 2.04 – 1.92 (m, 2H), 1.85 – 1.70 (m, 4H), 1.56 – 1.44 (m, 2H), 1.28 – 1.09 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 143.0, 139.0, 138.9, 129.8 (2), 127.0 (2), 116.8, 56.4, 39.1, 35.9, 34.5, 28.1, 25.7, 24.2, 21.7; IR (thin film): 1598 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{16}H_{22}NO_2S$ $[M+H]^+$: 292.1371, found: 292.1367

Supporting Information

Copies of ^{1}H and ^{13}C spectra for all new compounds and chiral HPLC traces for β-lactones **8a**, **8b**, **8d**, **8e**, and **8g**.

ACKNOWLEDGMENT

Support from the NSF (CHE-1546973) and the Robert A. Welch Foundation (AA-1280) are gratefully acknowledged. We thank Dr. Chang Suk Lee who performed early preliminary studies of applying the NCAL process toward *N*-heterocycle fused-β-lactones employing *N*-linked ketoacids. This work was initiated at Texas A&M University, Department of Chemistry and completed at Baylor University.

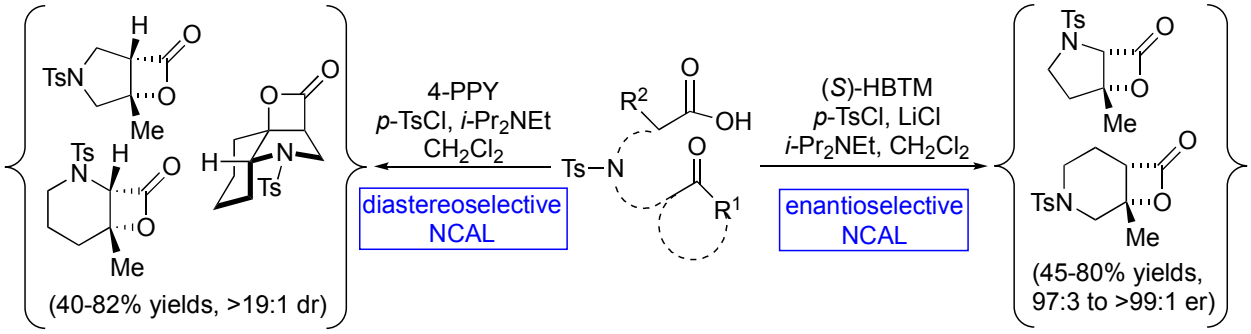
References:

(1) Wang, Y. T., R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605.

(2) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.
(3) Böttcher, T.; Sieber, S. A. *ChemMedChem* **2009**, *4*, 1260.
(4) Song, R.; Peng, W.; Zhang, Y.; Lv, F.; Wu, H.-K.; Guo, J.; Cao, Y.; Pi, Y.; Zhang, X.; Jin, L. *Nature* **2013**, *494*, 375.
(5) Gersch, M.; Famulla, K.; Dahmen, M.; Göbl, C.; Malik, I.; Richter, K.; Korotkov, V. S.; Sass, P.; Rübsamen-Schaeff, H.; Madl, T. *Nat. Comm.* **2015**, *6*, 6320.
(6) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945.
(7) Wynberg, H.; Staring, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 166.
(8) Van, K. N.; Morrill, L. C.; Smith, A. D.; Romo, D. In *Lewis Base Catalysis in Organic Synthesis* 2016, p 527.
(9) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 9479.
(10) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348.
(11) Harvey, N. L.; Krysiak, J.; Chamni, S.; Cho, S. W.; Sieber, S. A.; Romo, D. *Chem. Eur. J.* **2015**, *21*, 1425.
(12) Ma, Y.; Qu, L.; Liu, Z.; Zhang, L.; Yang, Z.; Zhang, L. *Curr. Top. Med. Chem.* **2011**, *11*, 2906.
(13) Feng, Y.; Majireck, M. M.; Weinreb, S. M. *Angew. Chem. Int. Ed.* **2012**, *124*, 13018.
(14) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764.
(15) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, *76*, 2.
(16) Sikriwal, D.; Dikshit, D. K. *Tetrahedron* **2011**, *67*, 210.
(17) Liu, G.; Romo, D. *Angew. Chem. Int. Ed.* **2011**, *123*, 7679.
(18) Liu, G.; Shirley, M. E.; Romo, D. *J. Org. Chem.* **2012**, *77*, 2496.
(19) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.
(20) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37.
(21) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214.
(22) Cheng, H.-Y.; Sun, C.-S.; Hou, D.-R. *J. Org. Chem.* **2007**, *72*, 2674.
(23) Yoshitomi, Y.; Makino, K.; Hamada, Y. *Org. Lett.* **2007**, *9*, 2457.
(24) Fidan, I.; Salmas, R. E.; Arslan, M.; Şentürk, M.; Durdagi, S.; Ekinci, D.; Şentürk, E.; Coşgun, S.; Supuran, C. T. *Biorg. Med. Chem.* **2015**, *23*, 7353.
(25) Adler, P.; Fadel, A.; Prunet, J.; Rabasso, N. *Org. Biomol. Chem* **2017**, *15*, 387.
(26) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270.
(27) Kinoshita, H.; Inomata, K.; Hayashi, M.; Kondoh, T.; Kotake, H. *Chem. Lett.* **1986**, *15*, 1033.
(28) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351.
(29) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115.
(30) Robinson, E. R.; Fallan, C.; Simal, C.; Slawin, A. M.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 2193.
(31) Stark, D. G.; Young, C. M.; O'Riordan, T. J.; Slawin, A. M.; Smith, A. D. *Org. Biomol. Chem* **2016**, *14*, 8068.
(32) Smith, S. R.; Fallan, C.; Taylor, J. E.; McLennan, R.; Daniels, D. S.; Morrill, L. C.; Slawin, A. M.; Smith, A. D. *Chem. Eur. J.* **2015**, *21*, 10530.
(33) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146.

(34) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714.
(35) Sreekumar Vellalath, P.; Romo, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 13934.
(36) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.
(37) Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049.
(38) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627.
(39) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771.
(40) Vellalath, S.; Van, K. N.; Romo, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 13688.
(41) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363.
(42) Miller, L. C.; Sarpong, R. *Chem. Soc. Rev.* **2011**, *40*, 4550.
(43) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *Chem. Sci.* **2017**, *8*, 1511.
(44) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478.
(45) Mulzer, J.; Hoyer, K.; Müller-Fahrnow, A. *Angewandte Chemie International Edition in English* **1997**, *36*, 1476.

TOC Entry


4-PPY
p-TsCl, i-Pr2NEt
CH2Cl2
diastereoselective NCAL
(40-82% yields, >19:1 dr)
(S)-HBTM
p-TsCl, LiCl
i-Pr2NEt, CH2Cl2
enantioselective NCAL
(45-80% yields, 97:3 to >99:1 er)