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NITROOLEFINS IN ONE-FLASK, TANDEM, A+B+C COUPLING REACTIONS PRODUCING HETEROCYCLES

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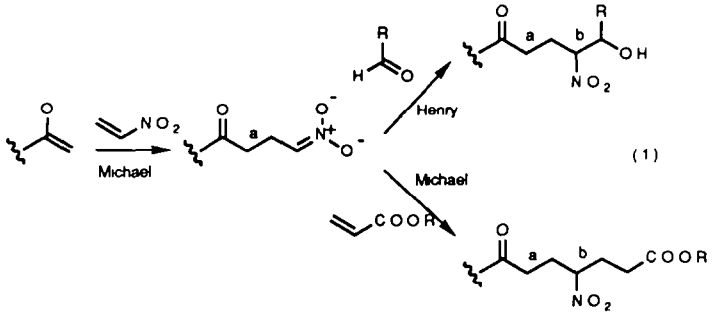
Abstract- Nitroolefins are shown to be effective Michael acceptor B units in sequential, convenient, multi-gram scale A+B+C coupling in one reaction vessel to produce nitroalkane intermediates that are converted into oxygen and nitrogen heterocycles. The sequence is initiated by enolate nucleophiles (A) and is terminated by aldehydes or acrylate electrophiles (C). The utility of this protocol for rapid assembly of complex structures from simple and readily available components is illustrated by a short total synthesis of a pyrrolizidine alkaloid.

The classical Robinson tropane alkaloid synthesis is a beautiful example of constructing a natural heterocycle by sequentially and efficiently joining several different components in one reaction vessel.[1] Our interest in such multicomponent, one-pot, annulation reactions has involved three- and four- component processes leading to carbocycles and to heterocycles.[2] We report now use of nitroolefins as the second (B) component in A+B+C coupling processes initiated by enolate ions A and terminated by C components such as aldehydes or acrylates (eq. 1); two new carbon-carbon bonds a and b are formed in this way, and structurally and functionally complex nitroalkanes are produced allowing subsequent use of the rich chemistry of the nitro group.[3]



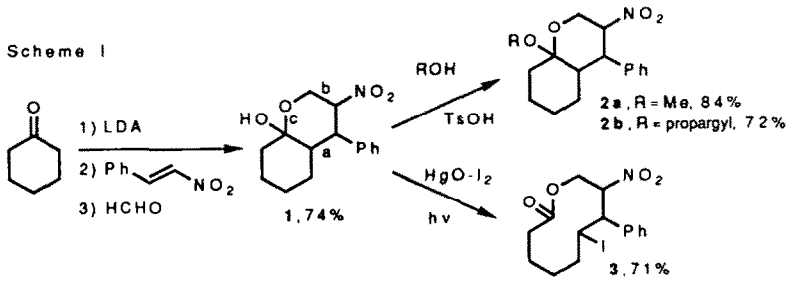
(1)

Results and Discussion

Ketone Enolate Initiators

The lithium enolate of cyclopentanone, cyclohexanone, and cycloheptanone reacted rapidly with commercially available β-nitrostyrene under aprotic conditions in THF at -78° to form in situ a nitronate to which was added formaldehyde. The initial β-nitroethanol Henry adduct[4] in the cyclohexanone case underwent spontaneous cyclization via hemiketal formation;[5] six-membered oxygen heterocycle **1**, formed globally in a 2+2+2 assembly (bonds a, b, c),[2d] was isolated in 74% yield as a 6:1 mixture of diastereomers (Scheme I). Good precedent exists for such stereoselectivity in Michael additions to nitroolefins.[6] Pyranose hemiketal **1** underwent smooth alcoholysis with methanol and with propargyl alcohol to form mixed ketals **2a** and **2b** in 84 and 72% yields, respectively. Propargylic ketal nitroalkane **2b** was exposed to radical-forming conditions (Bu_3SnH, AIBN);[3c, 7] although the nitro group was indeed removed (and replaced by a hydrogen atom), no intramolecular addition of an intermediate carbon-centered radical to the pendant propargylic group was detected. Photolysis of hemiketal **1** in the presence of mercuric oxide and iodine[8] gave functionalized macrolide **3** in 71% yield. In these ways then, some simple acyclic building blocks were converted rapidly and efficiently into structurally much more complex heterocycles.

Scheme I

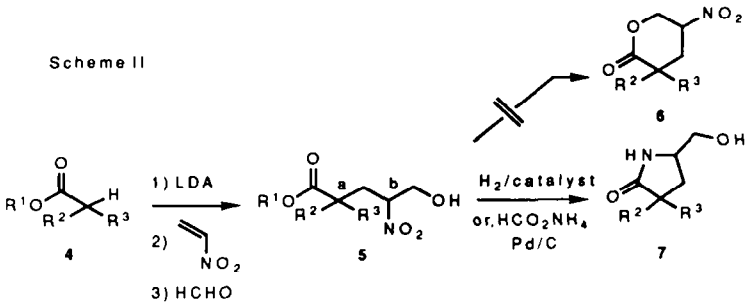


Ester Enolate Initiators and Aldehyde Terminators

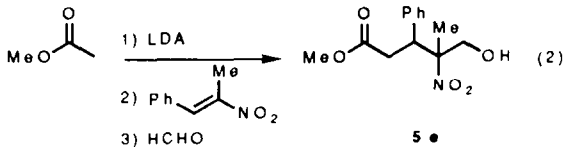
The lithium enolates of several different acetate esters **4** reacted rapidly with nitroethylene[9] at -78° in THF and subsequently with formaldehyde in Henry nitroaldol fashion[4] to form 5-hydroxyalkanoate esters **5** in good yields (Scheme II). Surprisingly, attempts to cyclize hydroxyesters **5** into lactones **6** under basic, acidic, or even neutral conditions[10] were uniformly unsuccessful. To exclude the possibility that the high acidity of the CH-NO_2 proton in hydroxyesters **5** was interfering with the lactonization process, eq. 2 was performed successfully to produce a tertiary nitroalkane, but no lactone product was detected. In contrast to these failed cyclizations, catalytic hydrogenation,[11] transfer hydrogenation,[12] and nickel boride[13] reduction of the nitro functionality in esters **5** proceeded smoothly to produce heterocycles **7** after heating.

Thus hydroxymethylpyrrolidinone lactams **7** were formed in 31-39% overall yields in only two steps from simple acyclic precursors.

Scheme II

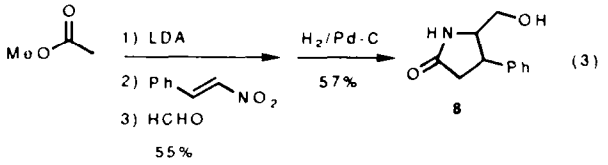


	B^1	B^2	B^3	yield of 5	yield of 7
a)	Me	Ph	H	77%	40%
b)	Me	PhS	H	65%	-
c)	Me	Me	Me	48%	81%
d)	Et	Me	Me	74%	49%



(2)

With commercially available β-nitrostyrene instead of nitroethylene as the B component, A+B+C coupling and reductive cyclization produced vicinally disubstituted lactam **8** (eq. 3) that has been converted previously into several different natural products having medicinal value.[14]

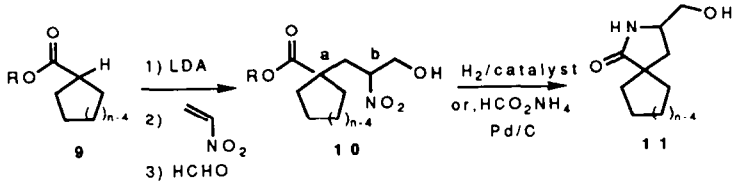


(3)

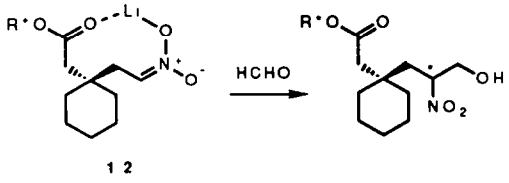
In a similar fashion, cycloalkanecarboxylate esters **9** of ring sizes from 7-4 were transformed into spirobicyclic heterocycles **11** (Scheme III).[15] Methyl

cyclohexanecarboxylate, for example, initiated this A+B+C protocol and produced nitro ester **10b** on gram scale. Replacement of the methyl ester group in this initial Michael donor **9b** by several different simple and chelating chiral alcohols (e.g. 2-octanol, 1-phenybutanol, N-methylprolinol, 1,1'-binaphthol monomethylether) was done to explore whether intermediate nitronates such as **12** would be subject to asymmetric induction during attachment of the terminating aldehyde C component. Unfortunately, no evidence for such asymmetric induction (e.g. diastereomeric excess) was found. Oxidation of primary alcohols **11** would produce spirobicyclic pyroglutamic acids that might be useful after resolution as chiral auxiliaries of greater rigidity than already useful pyroglutamic acid itself.[16] Reduction[17] of lactams **11** would produce spirobicyclic prolinols that might be useful after resolution as more rigid chiral auxiliaries than already useful prolinol itself and other prolinol derivatives.[18] A more complex example of this type of A+B+C coupling is shown in eq. 4 in which hydroxydiester **13** was isolated in 52% yield as a 5:4:2 mixture of stereoisomers.

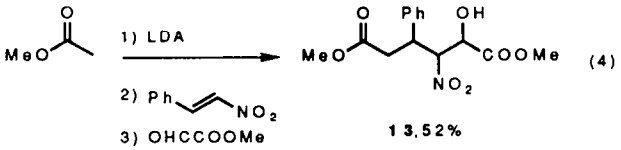
Scheme III



	B	n	yield of **10**	yield of **11**
a)	Me	7	56%	49%
b)	Me	6	67%	83%
c)	Me	5	56%	59%
d)	Et	4	56%	33%



12



13, 52%

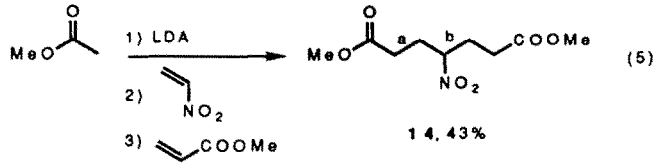
Attempts to raise the yields of the terminating nitroaldol step by adding KOBu-t/t-BuOH to the intermediate nitronates, in accord with substantial literature analogy on nitroaldol reactions in protic media, [4,19] failed to provide better results than those shown in Scheme II.

Thus, ester enolate-initiated Michael addition to nitroolefins followed by in situ Henry aldol termination with aldehydes allows convenient and rapid assembly of useful lactams that are 3-monosubstituted, 3,3-disubstituted (Scheme II) and also 4,5-disubstituted (eq. 3).

Ester Enolate Initiators and Acrylate Terminators

Under aprotic conditions, A+B+C Michael addition of ester enolates to nitroethylene followed by Michael addition of the intermediate nitronate anion to methyl acrylate at a temperature of at least 50°C in THF proceeded in a modest 43% yield (eq. 5). Attempts to improve the yield of this procedure using cosolvents (e.g. HMPA, N-methylpyrrolidone) or Lewis acids (e.g. $BF_3 \bullet OEt_2$) were not successful. Although there are many literature reports on nitronate anion Michael additions to acrylates in polar protic media,[20] there are very few reports indeed on such additions in aprotic media.[21] When the third component C was changed to a methylenemalonate ester, then A+B+C coupling occurred in a slightly better 55% yield (eq. 6). Because unsubstituted acetate esters are prone to condense easily with ester enolate ions, we chose methyl 2-phenylthioacetate enolate as a more stable initiator; Michael addition to nitroethylene and subsequent Michael addition to doubly-activated 1,1-disubstituted propenes gave A+B+C 1,7-dicarbonyl ester coupling products on multi-gram scale in very good to excellent yields (eq. 7). Although a mixture of diastereomers was formed in eq. 7, nickel boride in refluxing methanol[13c] caused reductive cleavage of both phenylthio groups in adduct **16d**, for example, and also reduction of the nitro group into an amine that underwent smooth in situ cyclization to a mixture of lactams **17** in 57%

yield. Other reduction procedures were much less successful than $NiCl_2/NaBH_4$; the nitro group was not reduced by $Fe/HOAc$[22] or by Al/Hg,[23] and Raney nickel [24] failed to desulfurize the α-phenylthio ester **16d**. Further cyclization[25] produced imides **18** in 76% yield. Pyrrolizidinediones like imide **18** have been used as potent amnesia reversing agents.[25]



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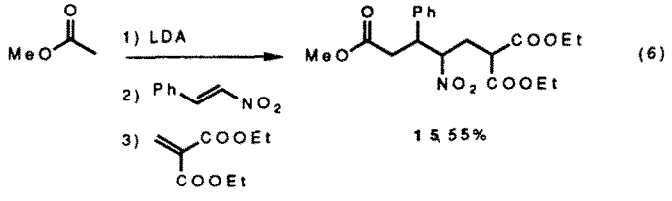

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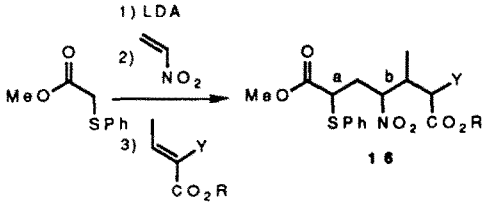
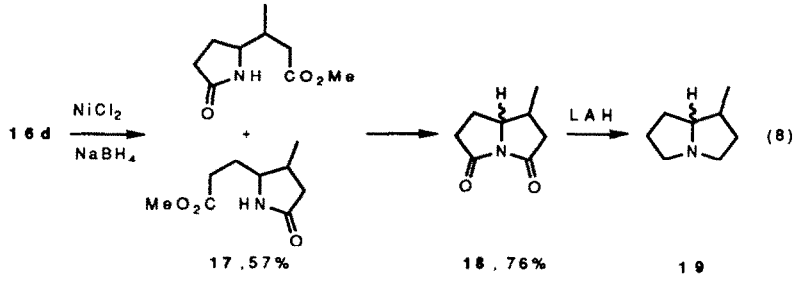


(7)

	R	Y	yield 16
a)	Me	CO_2Me	62%
b)	Et	CO_2Et	90%
c)	Me	SO_2Tol	73%
d)	Me	SPh	78%

Lithium aluminum hydride reduction[26] afforded pyrrolizidine alkaloid (±)-**19** as a 2.4:1.0 mixture of isomers in 81% yield (eq. 8).[27] The overall yield of natural heterocycle **19** in 4 simple steps from readily available acyclic components is 27% (78 x 57 x 76 x 81). This A+B+C approach to pyrrolizidine alkaloid **19** is much milder and conceptually complementary to the Leonard A+B+C approach[28] in which nitromethane was used as the pivotal A Michael donor and crotonate and then acrylate esters were the

B and C Michael acceptors; Leonard's synthesis, although very successful, culminated in an extremely harsh (i.e. 250°C, 300 atmospheres of hydrogen) catalytic hydrogenation reaction using copper chromite and requiring specialized equipment. Our attempts to prepare hydroxymethylpyrrolizidines via A+B+C coupling terminated by acrylate components C such as 2-phenylthio- and 2-phenylsulfonyl-2-butenolides were not successful.



In summary, an effective procedure has been developed for using nitroolefins as B units in tandem A+B+C coupling reactions in one reaction vessel leading rapidly and conveniently to functionalized nitroalkanes. Particularly mild and effective conditions have been developed using especially nickel boride for reduction of nitroester intermediates leading directly and conveniently to lactam heterocycles. This one-flask, multicomponent protocol followed by manipulation of the nitro group in the intermediate nitroalkanes allows easy conversion of simple and readily available reactants into products that are much more complex structurally and much richer in functionality and therefore that are useful as advanced synthetic intermediates.

Acknowledgment

We thank the National Science Foundation (CHE-86-07974) and the Petroleum Research Fund, administered by the American Chemical Society, for financial support.

Experimental

Melting points are uncorrected. NMR spectra were recorded on a Varian CFT-20 (80 MHz) and/or a Varian XL-400 (400 MHz) instrument using $CDCl_3$ or tetramethylsilane as an internal standard. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad. Infrared spectra were obtained using a Perkin-Elmer 599-B or a Perkin-Elmer 1600 Series FT-IR using the 1601 cm^{-1} band of polystyrene as a reference. Mass spectra were recorded on a two

sector high resolution VG Instruments 70-S instrument at 70 eV. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia.

All reagents were obtained from Aldrich and used as received except where noted. Nitroethylene was prepared via the method of Ranganathan.[9] n-BuLi was titrated with 2,5-dimethoxybenzyl alcohol. THF was freshly distilled from sodium benzophenone ketyl. Diisopropylamine was distilled from CaH_2.

Cyclohexanone Hemiketal 1: To an oven dried, 3-necked, 50 mL round bottom flask fitted with a magnetic stir bar and rubber septa and charged with Argon was added diisopropylamine (690 μL, 4.95 mmol, 1.10 eq) and THF (30 mL). After cooling to 0°C, n-BuLi (3000 μL of 1.58M in hexanes, 4.74 mmol, 1.05 eq) was added dropwise followed by stirring for 10 min. The mixture was cooled to -78°C and cyclohexanone (470 μL, 4.50 mmol, 1.00 eq) was added dropwise. After 1 h, a solution of β-nitrostyrene (800 mg, 5.40 mmol, 1.20 eq) in THF (3 mL) was added via cannula and the reaction mixture rapidly turned brown. Stirring for 3 h at -78°C was followed by warming to -15°C. Gaseous formaldehyde was added in a stream of nitrogen from paraformaldehyde heated to 155 - 160°C. Addition of formaldehyde continued until the reaction mixture was cloudy. Stirring continued for 30 min at -15°C and quenching was achieved by adding saturated aqueous NH_4Cl (10 mL) and warming to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 1.61 g of crude product which upon column chromatography (solvent gradient: 25 - 50% Et_2O/hexanes) yielded 771.3 mg of **1** as a white solid (63%, mp: 170 - 172°C) ^1H NMR: ($CDCl_3$) δ 7.33 - 7.16 (m, 5H), 4.72 (m, 1H), 4.57 (dd, J = 13.26, 3.36 Hz, 1H), 4.10 (dd, J = 13.26, 0.92 Hz, 1H), 3.40 (dd, J = 18.80, 4.46 Hz, 1H), 2.83 (dt, 1H), 1.89 - 0.85 (m, 8H); IR: ($CHCl_3$, cm^{-1}) 3570, 2930, 1550; mp: 173 - 174°C after recrystallization from benzene/hexanes; Analysis: calculated for $C_{15}H_{19}NO_4$: C, 64.98%; H, 6.86%; N; 5.05%; found: C, 65.06%; H, 6.94%; N, 4.97% A second fraction of 135 mg (11%, mp: 160 - 162°C) had similar spectral characteristics.

Ketal 2a: To a mixture of hemiketal **1** (8.3 mg, 0.03 mmol, 1.0 eq) and catalytic p-toluenesulfonic acid under Argon in a dry 2 mL vial fitted with a magnetic stir bar and rubber septum was added methanol (1 mL). The mixture stirred for 24 hours at room temperature and was diluted with Et_2O (10 mL) and washed with saturated aqueous $NaHCO_3$ (1 x 5 mL), dried with $MgSO_4$, filtered, and concentrated to yield 7.3 mg (84%) of ketal **2a** as a colorless oil. ^1H NMR: ($CDCl_3$) δ 7.40 - 7.10 (m, 5H), 4.70 (m, 1H), 4.10 (m, 1H), 3.45 (dd, 1H), 3.25 (s, 3H), 2.83 (dt, 1H), 2.12 (br d, 1H), 1.80 - 1.10 (m, 7H); IR: ($CHCl_3$, cm^{-1}) 2930, 1545

Ketal 2b: To an oven dried, 10 mL round bottom flask fitted with a magnetic stir bar and a rubber septum containing **1** (100 mg, 0.36 mmol, 1.0 eq) and catalytic p-toluenesulfonic acid under Argon was added propargyl alcohol (8 mL). The mixture stirred overnight at room temperature and was diluted to 20 mL with Et_2O, washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), dried with $MgSO_4$, filtered, and concentrated to yield 128.3 mg of crude product. After preparative TLC (eluting solvent: 30% Et_2O/hexanes), 81.8 mg (72%) of **2b** was isolated as a colorless oil. ^1H NMR: ($CDCl_3$) δ 7.40 - 7.25 (m, 5H), 4.78 (m, 1H), 4.19 (m, 2H), 3.45 (dd, 1H), 2.83 (dt, 1H), 2.45 (s, 1H), 2.04 (s, 2H), 1.80 - 1.30 (m, 8H); IR: ($CHCl_3$, cm^{-1}) 3300, 2940, 2870, 1550

Macrolide 3: A dry 10 mL round bottom flask fitted with a magnetic stir bar was charged with hemiketal **1** (31.7 mg, 0.114 mmol, 1.0 eq), pyridine (46 µL, 0.57 mmol, 5.0 eq), and benzene (9 mL). To this mixture was added, all at once, red HgO (60 mg, 0.27 mmol, 2.4 eq) and I_2 (59 mg, 0.23 mmol, 2.0 eq, J. T. Baker). Irradiation with a 275 watt sunlamp proceeded overnight. The mixture was cooled to room temperature and Et_2O was added to bring the volume to 20 mL. The mixture was filtered through Celite and washed with saturated sodium thiosulfate (1 x 25 mL), 5% HCl (3 x 25 mL), and water (2 x 25 mL), and dried with $MgSO_4$, filtered, and concentrated to yield 32.3 mg (70%) of **3** as a white solid (mp: 173 - 175°C). ^1H NMR: ($CDCl_3$) δ 7.50 - 7.10 (m, 5H), 5.40 (m, 1H), 5.05 (dd, 1H), 4.85 (t, 1H), 4.35 (t, 1H), 4.15 (dd, 1H), 2.72 (m, 1H), 2.45 - 1.62 (m, 7H); IR: ($CHCl_3$, cm^{-1}) 2970, 2860, 1735, 1550; Analysis: calculated for $C_{15}H_{18}INO_4$: C, 44.66%; H, 4.47%; found: C, 44.85%; H, 4.52%.

Methyl 5-Hydroxy-4-nitro-2-phenylmercaptopentanoate (5b): To a three-necked, 25 mL flask fitted with rubber septa and a magnetic stir bar and charged with diisopropylamine (322 µL, 2.30 mmol, 1.15 eq) and THF (10 mL) was added, dropwise, n-BuLi (1420 µL of 1.55 M in hexanes, 2.20 mmol, 1.10 eq) at 0°C. After 8 min, the mixture was cooled to -78°C and methyl α-phenylthioacetate (288 µL, 2.00 mmol, 1.00 eq) was added. Stirring was continued for 60 min when a solution of nitroethylene (185 mg, 2.43 mmol, 1.27 eq) in THF (2 mL) was added via cannula. After stirring for 90 min at -78°C, the reaction mixture was warmed to -20°C and gaseous formaldehyde was added in a stream of nitrogen from paraformaldehyde heated to 155 - 160 °C. Formaldehyde addition continued until the reaction mixture turned cloudy. The mixture was stirred at -20°C for 30 min. Quenching was achieved by addition of saturated aqueous NH_4Cl (5 mL) and warming to room temperature. Separation of layers was followed by extraction of the aqueous layer with ether (2 x 25 mL), CH_2Cl_2 (2 x 25

mL), and EtOAc (2 x 25 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to give 613 mg of crude product which, after column chromatography (10 g silica gel, 50% ether/hexanes), yielded 372.5 mg (65% as a mixture of diastereomers) of **5b**. ^1H NMR: ($CDCl_3$) δ 7.35 (m, 2H), 7.27 (m, 3H), 5.00, 4.63 (m, 1H), 3.98 (m, 2H), 3.69, 3.66 (s, 3H), 3.64 (m, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 2.30, 2.11 (m, 1H); IR ($CHCl_3$, cm^{-1}): 3602, 3518, 2954, 1735, 1559

Methyl 5-Hydroxy-4-nitro-2-phenylpentanoate (5a): Methyl α-phenylacetate (300 mg, 2.00 mmol) was treated as above to give 388 mg of **5a** (77%, as a mixture of diastereomers). ^1H NMR: ($CDCl_3$) δ 7.45 - 7.20 (m, 5H), 4.65, 4.35 (m, 1H), 4.00 (m, 2H), 3.70, 3.60 (s, 3H), 2.70, 2.55 (m, 1H), 2.40 - 2.20 (m, 3H); IR ($CHCl_3$, cm^{-1}): 3486, 2954, 1732, 1552; HRMS: calculated for $C_{12}H_{15}NO_5$ (M^+): 253.0950; found: 253.0951.

Methyl 2,2-Dimethyl-5-hydroxy-4-nitropentanoate (5c): Methyl isobutyrate (153 mg, 1.50 mmol) gave 147.1 mg of adduct **5c** (48%). ^1H NMR: ($CDCl_3$) δ 4.70 (m, 1H), 3.91 (m, 2H), 3.67 (s, 3H), 2.29 (dd, 1H), 1.95 (dd, 1H), 1.23 (s, 6H); IR ($CHCl_3$, cm^{-1}): 3602, 3489, 2979, 2954, 1724, 1553

Ethyl 2,2-dimethyl-5-hydroxy-4-nitropentanoate (5d): Ethyl isobutyrate (174 mg, 1.50 mmol) yielded 104.5 mg of adduct **5d** (74%) ^1H NMR: ($CDCl_3$) δ 4.68 (m, 1H), 4.10 (q, 2H), 3.90 (m, 2H), 2.60 (br s, 1H), 2.26 (dd, 1H), 1.97 (dd, 1H), 1.22 (m, 9H); IR ($CHCl_3$, cm^{-1}): 2963, 1732, 1558

Methyl 4-(Hydroxymethyl)-4-nitro-3-phenylpentanoate (5e): To an oven dried 2-necked 25 mL round bottom flask fitted with a magnetic stir bar and rubber septa and containing diisopropylamine (230 μL, 1.65 mmol, 1.10 eq) and THF (10 mL) at 0°C under Argon was added, dropwise, n-BuLi (1000 μL of 1.58 M in hexanes, 1.58 mmol, 1.05 eq). After stirring for 8 min, the mixture was cooled to -78°C and methyl acetate (120 μL, 1.50 mmol, 1.00 eq) was added and stirred for 45 min. A solution of 1-phenyl-2-nitropropene (293 mg, 1.80 mmol, 1.20 eq, Alfa) in THF (2 mL) was added via cannula. The mixture stirred for 90 min and was then warmed to -20°C. Gaseous HCHO was added in a nitrogen stream until the reaction mixture was cloudy. After stirring an additional 20 min, quenching was achieved by addition of saturated aqueous NH_4Cl (6 mL) with warming to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 522 mg of crude product. Column chromatography (solvent: 10 - 30% EtOAc/hexanes) of 213 mg of crude product yielded

187.6 mg (57%) of a major diastereomer **5e** and 67.8 mg (21%) of a minor diastereomer
Major diastereomer: ^{1}H NMR: ($CDCl_3$) δ 7.31 (m, 5H), 4.07 (dd, J = 14.01, 4.04 Hz, 1H), 3.90 (m, 1H), 3.52 (m, 1H), 3.50 (s, 3H), 2.92 (m, 1H), 2.65 (dd, J = 15.99, 4.27 Hz, 1H), 2.34 (s, 1H), 1.55 (s, 3H); IR: ($CHCl_3$, cm^{-1}) 3606, 1736, 1542; HRMS: calculated for $C_{13}H_{17}NO_5$ (M^+): 267.1107; found 267.1105
Minor diastereomer: ^{1}H NMR: ($CDCl_3$) δ 7.31 (m, 5H), 3.96 (m, 2H), 3.84 (d, J = 13.06 Hz, 1H), 3.51 (s, 3H), 2.93 (m, 1H), 2.78 (dd, J = 16.15, 3.90 Hz, 1H), 2.55 (m, 1H), 1.49 (s, 3H); IR: ($CHCl_3$, cm^{-1}) 3593, 3029, 2913, 1739, 1544; HRMS: calculated for $C_{13}H_{17}NO_5$ (M^+): 267.1107; found: 267.1110

5-Hydroxymethyl-3-phenyl-2-pyrrolidinone (7a): A mixture of methyl 5-hydroxy-4-nitro-2-phenyl-pentanoate **5a** (343 mg, 1.36 mmol, 1.00 eq) and W-2 Raney Nickel (90 mg, W. R. Grace) in methanol (32 mL) was hydrogenated in a Parr 4561 apparatus at 1200 psi for 40 hours. After filtering through Celite, the alcoholic solution was heated to reflux for 4 hours, cooled, and concentrated to give 243.6 mg of crude material. Crystallization from CH_2Cl_2/pentane gave 68.1 mg of desired product as a white solid (mp: 136 - 138°C). A second crop gave an additional 20.4 mg of product (136 - 138°C) for a total yield of 32%. ^{1}H nmr: ($CDCl_3$) δ 7.35 (m, 5H), 6.45 (br s, 1H), 3.85 (m, 1H), 3.75 (m, 2H), 3.55 (m, 1H), 2.35 (m, 2H); IR: ($CHCl_3$, cm^{-1}) 3430, 3008, 2932, 1698; HRMS: calculated for $C_{11}H_{13}NO_2$ (M^+): 191.0946; found: 191.0947.

3,3-Dimethyl-5-hydroxymethyl-2-pyrrolidinone (7c): To a 10 mL flask containing a stirring mixture of ethyl 2,2-dimethyl-5-hydroxy-4-nitro-pentanoate **5c** (146 mg, 0.716 mmol, 1.00 eq) and 10% Pd/C (36 mg) was added ammonium formate (380 mg, 6.03 mmol, 8.42 eq). The mixture stirred overnight under N_2. After filtering through Celite, the mixture was heated to reflux over 4 h. The solution was cooled to room temperature and concentrated to give, after column chromatography (2 - 5% MeOH/CH_2Cl_2), 83.3 mg (81%) of lactam **7c**. ^{1}H NMR: ($CDCl_3$) δ 4.20 (dd, 1H), 3.80 (t, 2H), 3.36 (d, 1H), 2.04 (dd, 1H), 1.87 (dd, 1H), 1.18 (d, 6H); IR: ($CHCl_3$, cm^{-1}) 3435, 2974, 2876, 1668, 1459; HRMS: calculated for $C_7H_{13}NO_2$ (M^+): 143.0946; found: 143.0948.

Methyl 5-hydroxy-4-nitro-3-phenylpentanoate: To an oven dried, 3-necked, 50 mL round bottom flask fitted with a magnetic stir bar and rubber septa and charged with diisopropylamine (690 μL, 4.95 mmol, 1.10 eq) and THF (25 mL) under Argon at 0°C was added, dropwise, n-BuLi (3000 μL of 1.58 M in hexanes, 4.74 mmol, 1.05 eq). After stirring for 8 min, the mixture was cooled to -78°C and methyl acetate (360 μL, 4.50

mmol, 1.00 eq) was added dropwise. Stirring for 1 h was followed by addition via cannula of a previously cooled (-78°C) solution of β-nitrostyrene (810 mg, 5.4 mmol, 1.20 eq) in THF (3 mL). The reaction mixture turned brown immediately. After 1 h, the reaction mixture was warmed to -15°C and gaseous formaldehyde was added in a stream of nitrogen until the solution turned cloudy. Stirring at -15°C continued for 30 min and quenching was achieved by adding saturated aqueous NH_4Cl (6 mL) and warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 1.49 g which, after column chromatography (solvent: 30 - 50% Et_2O/hexanes), yielded 430 mg of a major diastereomer of methyl 5-hydroxy-4-nitro-3-phenylpentanoate (38%) and 200.3 mg of a minor diastersomer (17%).
Major diastereomer: ^1H NMR: ($CDCl_3$) δ 7.35 - 7.20 (m, 5H), 4.85 (m, 1H), 3.86 - 3.74 (m, 1H), 3.61 (dd, J = 12.35, 3.05 Hz, 2H), 3.51 (s, 3H), 2.79 (dd, J = 16.02, 9.77 Hz, 1H), 2.67 (dd, J = 15.99, 4.58 Hz, 1H); IR: ($CHCl_3$, cm^{-1}) 3430, 1725, 1550; HRMS: Calculated for $C_{11}H_{12}NO_4$ ($M - OCH_3^+$): 222.0766; found: 222.0771
Minor diastereomer: ^1H NMR: ($CDCl_3$) δ 7.33 - 7.26 (m, 5H), 4.95 (dt, 1H), 4.02 (m, 2H), 3.84 (m, 2H), 3.61 (s, 3H), 2.90 (dd, 1H), 2.80 (dd, 1H); IR: ($CHCl_3$, cm^{-1}) 3500, 1725, 1545; HRMS: Calculated for $C_{12}H_{15}NO_5$ (M^+): 253.0950; found: 253.0958

5-(Hydroxymethyl)-4-phenyl-2-pyrrolidinone (8): To a 15 x 125 mm test tube fitted with a magnetic stir bar was added methyl 5-hydroxy-4-nitro-3-phenylpentanoate (108. mg, 0.430 mmol, 1.00eq), 10% Pd/C (35 mg), and methanol (1 mL). The test tube was placed in a hydrogenation apparatus (Fischer & Porter) and, as the mixture stirred, the apparatus was charged with H_2 and evacuated. After four such purgings, the apparatus was charged with H_2 at 42 psi and stirring continued overnight. The mixture was filtered through a Celite pad into a 10 mL round bottom flask. Methanol (3 mL) was added, a reflux condenser affixed, and the mixture was heated to reflux in an oil bath at 90 - 100°C overnight. Cooling to room temperature and evaporation of solvent gave 46.3 mg (57%) of **8** as a colorless oil. ^1H NMR: ($CDCl_3$) δ 7.33 (m, 5H), 6.70 (br s, 1H), 3.92 (m, 1H), 3.78 (m, 2H), 3.56 (m, 1H), 3.31 (m, 1H), 2.82 (dd, J = 17.31, 9.46, 1H), 2.57 (dd, J = 17.29, 8.58, 1H); IR: ($CHCl_3$, cm^{-1}) 3423, 3318, 1684; HRMS: calculated for $C_{11}H_{13}NO_2$ (M^+): 191.0946; found: 191.0947

A typical example of the synthesis of alkyl 5-hydroxy-4-nitro-2-spiroalkylpentanoate **10** is as follows:

Methyl 5-Hydroxy-4-nitro-2-spirocyclohexylpentanoate (10b): To an oven dried 25 mL two necked flask fitted with rubber septa and a magnetic stir bar and charged with

diisopropylamine (765 μL, 5.40 mmol, 1.20 eq) and THF (10 mL) under Ar with stirring at 0°C was added nBuLi (3300 μL of 1.58 M in hexanes, 5.20 mmol, 1.15 eq). After 7 min, the flask was cooled to -78°C and methyl cyclohexanecarboxylate (645 μL, 4.50 mmol, 1.00 eq) was added dropwise. After stirring at -78°C for 30 min, a solution of nitroethylene (430 mg, 5.85 mmol, 1.30 eq) in THF (3 mL) was added via cannula. The resultant bright yellow solution stirred at -78°C for 30 min then was warmed to -20°C. Gaseous formaldehyde was added in a stream of N_2 from paraformaldehyde heated to 155 - 160°C. Formaldehyde addition was stopped when the reaction mixture was cloudy. After an additional 15 min, quenching was achieved by addition of saturated ammonium chloride (5 mL) and warming to room temperature. Separation of layers was followed by extraction of the aqueous layer with Et_2O (2 x 25 mL), CH_2Cl_2 (2 x 25 mL) and EtOAc (2 x 25 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 1340 mg of crude product. Column chromatography (15 g silica gel, 30% Et_2O/hexanes) yielded 742 mg (67%) of desired product, **10b**, as a pale yellow oil. ^1H NMR: ($CDCl_3$) δ 4.68 (m, 1H), 3.95 - 3.80 (m, 2H), 3.67 (s, 3H), 2.35 (dd, 1H), 2.05 (m, 2H), 1.85 (dd, 1H), 1.53 (m, 3H), 1.40 - 1.15 (m, 6H); IR: ($CHCl_3$, cm^{-1}) 3609, 3494, 2939, 2860, 1724, 1556, 1454; HRMS: calculated for $C_{10}H_{16}O$ (M - OMe^+): 214.1079; found: 214.1082.

Methyl 5-Hydroxy-4-nitro-2-spirocycloheptylpentanoate (10a): Methyl cycloheptanecarboxylate (78.0 mg, 0.500 mmol) was treated as above to yield 71.1 mg (56%) of adduct **10a** as a yellow oil. ^1H NMR: ($CDCl_3$) δ 4.65 (m, 1H), 4.00 -3.80 (m, 2H), 3.67 (s, 3H), 2.34 (dd, 2H), 2.20 - 1.40 (m, 13H); IR ($CHCl_3$, cm^{-1}): 3615, 3504, 2932, 1725, 1557; HRMS: calculated for $C_{11}H_{18}NO_4$ (M - OMe^+): 228.1236; found: 228.1237.

Methyl 5-Hydroxy-4-nitro-2-spirocyclopentylpentanoate (10c): Methyl cyclopentanecarboxylate (188 mg, 1.45 mmol) was treated as above to yield 188 mg (56%) of adduct **10b** as a yellow oil. ^1H NMR: ($CDCl_3$) δ 4.63 (m, 1H), 3.89 (m, 2H), 3.67 (s, 3H), 2.42 (br m, 1H), 2.35 (dd, 1H), 2.20 - 1.10 (m, 9H); IR ($CHCl_3$, cm^{-1}): 3499, 2963, 1736, 1558; HRMS: calculated for $C_9H_{14}NO_4$ (M - OMe^+): 200.0923; found: 200.0925.

Ethyl 5-Hydroxy-4-nitro-2-spirocyclobutylpentanoate (10d): Ethyl cyclobutanecarboxylate (207μL, 1.50 mmol) was reacted as above to generate 195.3 mg (56%) of adduct **10d** as a yellow oil. ^1H NMR: ($CDCl_3$) δ 4.56 (m, 1H), 4.13 (q, 2H), 3.88 (m, 2H), 2.73 (br s, 1H), 2.43 (m, 3H), 2.20 (dd, 1H), 1.94 (m, 4H), 1.27 (t, 3H); IR ($CHCl_3$, cm^{-1}): 3610, 3489, 2985, 2943, 1719, 1556.

A typical procedure for the catalytic hydrogenation of **10** is as follows:

1-Oxo-2-aza-3-hydroxymethyl-spiro[4.5]decane (11b): A mixture of methyl 5-hydroxy-4-nitro-2-spirocyclohexylpentanoate **10b** (107 mg, 0.437 mmol, 1.00 eq) and Raney Nickel (30 mg, W. R. Grace) in methanol (27 mL) was placed in a Parr 4561 Reactor and, after repeated purging of air, was pressurized to 1300 psi with H_2. Hydrogenation proceeded overnight. The mixture was filtered through Celite, washing with methanol. The filtrate was heated to reflux for 4 hours, dried with Na_2SO_4, filtered, and concentrated to give 72.8 mg of crude product. Column chromatography (1.5 g silica gel, 50% EtOAc/CH_2Cl_2) yielded 47.7 mg (60%) of desired product, **11b**, as a white solid (mp: 132 - 133°C). ^1H NMR: ($CDCl_3$) δ 7.35 (br s, 1H), 4.40 (br s, 1H), 3.70 (m, 2H), 3.41 (dd, 1H), 2.14 (dd, 1H), 1.80 - 1.10 (m, 11H); IR: ($CHCl_3$, cm^{-1}) 3339, 2934, 2858, 1682, 1450; mp: 132.5 - 133.5°C (after recrystallization from CH_2Cl_2/hexanes); Analysis: calculated for $C_{10}H_{17}NO_2$: C, 65.57%; H, 9.29%; N, 7.65%; found: C, 65.46%; H, 9.39%; N, 7.65%

A typical hydrogen transfer reduction is described below:

1-Oxo-2-aza-3-hydroxymethyl-spiro[4.5]decane (11b): To an oven dried, 10 mL round bottom flask fitted with rubber septum and magnetic stir bar and containing methyl 5-hydroxy-4-nitro-2-spirocyclohexylpentanoate **10b** (161.2 mg, 0.658 mmol, 1.00 eq) in 50% methanol/THF (7 mL) was added, with stirring, 10% Pd/C (32 mg), followed by anhydrous ammonium formate (222 mg, 3.52 mmol, 5.35 eq). Gas evolution was observed within 10 minutes. Stirring under Argon continued for 6 h. The heterogeneous mixture was filtered through Celite and heated to reflux overnight. After cooling to room temperature, Et_2O (10 mL) was added followed by filtering through Celite. Concentration in vacuo gave 248 mg of an oil. Column chromatography (3 g silica gel, 50% EtOAc/CH_2Cl_2) yielded 99.8 mg (83%) of product as a white solid.

1-Oxo-2-aza-3-hydroxymethyl-2-spiro[4.6]undecane (11a): Methyl 5-hydroxy-4-nitro-2-spirocycloheptylpentanoate, **10a**, (65.7 mg, 0.250 mmol) was reduced as above to generate 24.3 mg of lactam **11a** (49%) as a white solid (mp: 94 - 96°C). ^1H NMR: ($CDCl_3$) δ 4.21 (d, 1H), 3.74 (t, 2H), 3.38 (br d, 1H), 1.95 (m, 2H), 1.90 - 1.40 (m, 12H); IR ($CHCl_3$, cm^{-1}): 3439, 2930, 1671, 1461; HRMS: calculated for $C_{11}H_{19}NO_2$ (M^+): 197.1416; found: 197.1418.

1-Oxo-2-aza-3-hydroxymethyl-2-spiro[4.4]nonane (11c): Methyl 5-hydroxy-4-nitro-2-spirocyclopentylpentanoate, **11c**, (81 mg, 0.350 mmol) was reduced via hydrogen transfer reduction as above to yield 34.9 mg (59%) of lactam **11c** as a colorless oil. ^{1}H NMR: ($CDCl_3$) δ 4.10 (dd, 1H), 3.78 (t, 1H), 3.38 (d, 1H), 2.03 (dd, 1H), 1.95 - 1.95 (m, 10 H); IR ($CHCl_3$, cm^{-1}): 3428, 2956, 1673, 1453; HRMS: calculated for $C_9H_{15}NO_2$ (M^+): 169.1103; found: 169.1105.

1-Oxo-2-aza-3-hydroxymethyl-2-spiro[4.3]octane (11d): Ethyl 5-hydroxy-4-nitro-2-spirocyclobutylpentanoate, **10d**, (148.7 mg, 0.640 mmol) was reduced via transfer hydrogenation as above to give 32.7 mg (33%) of lactam **11d** as a colorless oil. ^{1}H NMR: ($CDCl_3$) δ 4.21 (d, 1H), 3.79 (t, 2H), 3.40 (d, 1H), 2.45 - 1.90 (m, 8H); IR ($CHCl_3$, cm^{-1}): 3420, 2983, 2940, 1672, 1446; HRMS: calculated for $C_8H_{17}NO_2$ (M^+): 155.0946; found: 155.0944.

Dimethyl 2-Hydroxy-3-nitro-4-phenyl-1,6-hexandioate (13): To a dry 25 mL round bottom flask fitted with a rubber septum and magnetic stir bar and charged with diisopropylamine (230 μL, 1.65 mmol, 1.10 eq) in THF (10 mL) under Argon was added nBuLi in hexanes (1000 μL of 1.58 M in hexanes, 1.58 mmol, 1.05 eq) at 0°C. After 7 min, the solution was cooled to -78°C and methyl acetate (120 μL, 1.50 mmol, 1.00 eq) was added. After 5 min, a solution of β-nitrostyrene (265 mg, 1.80 mmol, 1.20 eq) in THF (2 mL) was added via cannula and stirred at -78°C for 3 h. A solution of methyl glyoxylate (188 mg, 2.10 mmol, 1.40 eq) in THF (1 mL) was added via cannula. After 1 h at -78°C, the cold bath was removed for 10 minutes. Quenching was achieved by addition of saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 x 10 mL), saturated with solid NaCl, and washed with EtOAc (2 x 10 mL), CH_2Cl_2 (2 x 10 mL), and $CHCl_3$ (1 x 10 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to yield 506 mg of crude product. Column chromatography (11 g silica gel, solvent gradient: 5 - 40% ether/hexanes) yielded 3 diastereomers in 52% yield.

first diastereomer: 110.5 mg (23.7%) as a colorless oil. TLC R_f 0.289 (50% Et_2O/hexanes) ^{1}H NMR: ($CDCl_3$) δ 7.34 (m, 5H), 5.14 (dd, 1H), 4.14 (m, 1H), 3.95 (m, 1H), 3.79 (s, 3H), 3.53 (s, 3H), 3.20 (d, 1H), 2.70 (m, 2H); IR ($CHCl_3$, cm^{-1}): 3531, 1745, 1555; HRMS: calculated for $C_{13}H_{14}NO_6$ (M - OMe^+): 280.0821; found: 280.0822

second diastereomer: 44.4 mg (9.52%) as a colorless oil. TLC R_f 0.220 (50% Et_2O/hexanes) ^{1}H NMR: ($CDCl_3$) δ 7.29 (m, 5H), 5.19 (dd, 1H), 4.29 (d, 1H), 4.19 (dt, 1H), 3.74 (s, 3H), 3.55 (s, 3H), 3.35 (s, 1H), 2.80 (dd, 1H), 2.67 (dd, 1H); IR ($CHCl_3$,

cm^{-1}): 3480, 1736, 1559; HRMS: calculated for $C_{13}H_{14}NO_6$ (M - OMe^+): 280.0821; found: 280.0825
third diastereomer: 89.8 mg (19.2%) as a colorless oil. TLC R_f 0.153 (50% Et_2O/hexanes) ^1H NMR: ($CDCl_3$) δ 7.30 (m, 5H), 5.30 (dd, 1H), 4.60 (dd, 1H), 4.08 (m, 1H), 3.84 (s, 3H), 3.60 (s, 3H), 3.30 (s, 1H), 3.05 (dd, 1H), 2.90 (dd, 1H); IR ($CHCl_3$, cm^{-1}): 3527, 1743, 1557; HRMS: calculated for $C_{13}H_{14}NO_6$ (M - OMe^+): 280.0821; found: 280.0822

4-Nitro-1,7-heptandioic acid dimethyl ester (14):
To an oven dried 2-necked 25 mL round bottom flask fitted with a reflux condenser, magnetic stir bar, and rubber septa and containing diisopropylamine (485 μL, 3.45 mmol, 1.15 eq) and THF (12 mL) under Argon at 0°C was added nBuLi (2100 μL of 1.58 M in hexanes, 3.30 mmol, 1.10 eq). After 10 min, the flask was cooled to -78°C and methyl acetate (238 μL, 3.00 mmol, 1.00 eq) was added and stirring continued for 40 min. A solution of nitroethylene (263 mg, 3.60 mmol, 1.20 eq) in THF (1 mL) was added via cannula. After 15 min at -78°C, the solution is warmed to 0°C for 15 min, and a solution of methyl acrylate (380 μL, 4.20 mmol, 1.40 eq) in THF (1 mL) was added dropwise. The reaction was slowly warmed to room temperature and, then, heated to reflux overnight. After cooling to room temperature, quenching was achieved by addition of saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 601 mg of crude product which upon purification by column chromatography (10% EtOAc/hexanes) yielded 300.3 mg (43%) of **14** as a pale yellow oil. ^1H NMR: ($CDCl_3$) δ 4.62 (m, 1H), 3.69 (s, 6H), 2.41 - 2.14 (m, 8H); IR: ($CHCl_3$, cm^{-1}) 3031, 2938, 1722, 1555
Malonate adduct 15: To an oven dried 25 ml round bottom flask fitted with rubber septa, magnetic stir bar, and reflux condenser and containing diisopropylamine (230 μL, 1.65 mmol, 1.10 eq) and THF (10 mL) at 0°C under Argon was added n-BuLi (1000 μL of 1.58 M in hexanes, 1.58 mmol, 1.05 eq). After 10 min, the mixture was cooled to -78°C and methyl acetate (120 μL, 1.50 mmol, 1.00 eq) was added. The mixture stirred for 8 min and a solution of β-nitrostyrene (270 mg, 1.80 mmol, 1.20 eq) in THF (2 mL) was added via cannula. The mixture stirred for 1 h at -78°C and a solution of diethyl methylene malonate (360 mg, 2.10 mmol, 1.40 eq) in THF (2 mL) was added via cannula. After 1 h, the reaction mixture was warmed to room temperature and stirring was maintained overnight. The mixture was then refluxed for 12 h, cooled to room temperature, and quenched with saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with ether (3 x 15 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 725 mg of crude

material. Column chromatography (10 g silica gel, 10% ether/hexanes) yielded 324 mg (55%) of a pale yellow oil, **15**. ^{1}H nmr: ($CDCl_3$) δ 7.40 - 7.20 (m, 5H), 4.90 (dt, 1H), 4.16 (m, 1H), 3.70 (dt, 1H), 3.52 (s, 3H), 3.20 (dd, 1H), 2.80 - 2.40 (m, 2H), 2.30 (m, 1H), 2.10 (m, 1H), 1.21 (m, 6H); IR ($CHCl_3$, cm^{-1}): 2957, 1749, 1552; HRMS: calculated for $C_{19}H_{25}O_6$ ($M-NO_2^+$): 349.1651; found: 349.1655

Adduct 16a: To a flame-dried 25 mL round bottom flask fitted with a magnetic stir bar and rubber septa and charged with diisopropylamine (230 μL, 1.65 mmol, 1.10 eq) and THF (5 mL) at 0°C under N_2 was added, dropwise, n-BuLi (1000 μL of 1.58 M in hexanes, 1.58 mmol, 1.05 eq). After 10 min at 0°C, the reaction mixture was cooled to -78°C and methyl α-phenylthioacetate (235 μL, 1.50 mmol, 1.00 eq, Fluka) was added. Stirring for 30 min at -78°C was followed by the addition of a solution of nitroethylene (140 mg, 1.92 mmol, 1.25 eq) in THF (1 mL). After 1 h, a solution of dimethyl ethylidene malonate (320 μL, 2.25 mmol, 1.50 eq) in THF (1 mL) was added via cannula. The mixture was allowed to gradually warm to room temperature overnight. Quenching was achieved by adding saturated aqueous NH_4Cl (4 mL). The layers were separated and the aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (2 x 20 mL) and EtOAc (2 x 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 884 mg of a brown oil. Preparative TLC (50% ether/hexanes) of 282 mg of the crude material yielded 123.1 mg (62%) of desired product, **16a**, as a mixture of diastereomers. ^{1}H nmr: ($CDCl_3$) δ 7.50- 7.30 (m, 5H), 5.25, 4.75, 4.65 (m, 1H), 3.85 - 3.70 (m, 10H), 3.60 (m, 1H), 3.35 (m, 1H), 3.00 (m, 1H), 2.75 - 2.40 (m, 1H), 1.00 (m, 3H); IR: ($CHCl_3$, cm^{-1}): 3027, 2956, 1752, 1736, 1552; HRMS: calculated for $C_{18}H_{23}NSO_8$ (M^+): 413.1144; found: 413.1148

Adduct 16b: To an oven-dried 25 mL round bottom flask fitted with a rubber septum and magnetic stir bar and containing diisopropylamine (0.690 mL, 4.95 mmol, 1.10 eq) in THF (12 mL) at 0°C under N_2 was added n-BuLi (3.00 mL of 1.58 M in hexanes, 4.74 mmol, 1.05 eq). After 10 min, the mixture was cooled to -78°C and methyl α-phenylthioacetate (0.705 mL, 4.50 mmol, 1.00 eq) was added. The mixture was stirred for 30 min at -78°C and a solution of nitroethylene (0.422 g, 5.76 mmol, 1.28 eq) in THF (2 mL) was added via cannula. After 1 h, a solution of diethyl ethylidene malonate (1.23 mL, 6.75 mmol, 1.50 eq) in THF (2 mL) was added via cannula and the reaction mixture was stirred at -20°C overnight. Quenching was achieved by the addition of saturated aqueous NH_4Cl (5 mL) and warming to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL), CH_2Cl_2 (2 x 20 mL), and EtOAc (2 x 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 2.89 g of crude product as a brown oil. Column

chromatography (40 g silica gel, solvent gradient: 15 - 25% ether/hexanes) yielded 1.79 g (90%) of desired product, **16b** a yellow oil, as a mixture of diastereomers. ^{1}H nmr: ($CDCl_3$) δ 7.50 - 7.30 (m, 5H), 5.25, 4.85, 4.70 (m, 1H), 4.20 (m, 4H), 3.71, 3.70, 3.69, 3.67 (m, 3H), 3.62 (dd, 1H), 3.50 (m, 1H), 3.00 (m, 1H), 2.70 - 2.60 (m, 2H), 1.26 (m, 6H), 1.05 (t, 3H); IR: ($CHCl_3$, cm^{-1}): 3019, 1732, 1552

Adduct 16c: To a flame-dried 25 mL round bottom flask fitted with a magnetic stir bar and rubber septum and containing diisopropylamine (125 μL, 0.88 mmol, 1.10 eq) in THF (5 mL) at 0°C under N_2 was added n-BuLi (530 μL of 1.58 M in hexanes, 0.84 mmol, 1.05 eq). Stirring for 10 min was followed by cooling to -78°C and the addition of methyl α-phenylthioacetate (125 μL, 0.80 mmol, 1.00 eq). After 30 min, a solution of nitroethylene (70 mg, 0.96 mmol, 1.20 eq) in THF (1 mL) was added via cannula. The mixture was maintained at -78°C for 1 h and a solution of ethyl 2-tolylsulfonyl-2-butenoate (313 mg, 1.17 mmol, 1.46 eq) in THF (1 mL) was added via cannula. The reaction mixture stirred at -20°C for 28 h. Quenching with saturated aqueous NH_4Cl (3 mL) and warming to room temperature was followed by separation of the layers and extraction of the aqueous layer with ether (2 x 20 mL), CH_2Cl_2 (2 x 20 mL), and EtOAc (2 x 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 510 mg of a brown oil. Column chromatography (10 g silica gel, 30% ether/hexanes) yielded 304 mg (73%) of a yellow oil, **16c**, as a mixture of diastereomers. ^{1}H nmr: ($CDCl_3$) δ 7 75 (m, 3H), 7.45 (m, 2H), 7.35 (m, 5H), 5.70, 5.40, 5.20, 5.10, 4.90, 4.70 (m, 1H), 4.20 - 3.90 (m, 2H), 3.85 (m, 1H), 3.70 - 3.65 (m, 3H), 3.50 , 3.10 (m, 1H), 2.45 (s, 3H), 1.50 - 0.80 (m, 8H); IR: ($CHCl_3$, cm^{-1}): 2981, 1736, 1552, 1147; HRMS: calculated for $C_{24}H_{29}NS_2O_8$ (M^+): 523.1335; found: 523.1340.

3-Methyl-4-nitro-2,6-bis(phenylthio)-heptan-1,7-dioic acid, dimethyl ester (16d): To a flame-dried 50 mL round bottom flask equipped with a magnetic stir bar and rubber septum and containing diisopropylamine (1.33 mL, 9.46 mmol, 1.10 eq) and THF (25 mL) under N_2 at 0°C was added, dropwise, n-BuLi (5.70 mL of 1.58 M in hexanes, 9.03 mmol, 1.05 eq). The mixture stirred for 10 min, was cooled to -78°C, and methyl α-phenylthioacetate (1.35 mL, 8.60 mmol, 1.00 eq) was added. After 30 min, a solution of nitroethylene (0.753 g, 10.3 mmol, 1.20 eq) in THF (1 mL) was added via cannula and the solution stirred at -78°C for 1 h. A solution of methyl 2-phenylthio-2-butenoate (2.50 g, 12.0 mmol, 1.39 eq) in THF (3 mL) was added via cannula and the reaction mixture was allowed to warm to room temperature overnight. Quenching with saturated aqueous NH_4Cl (7 mL) was followed by separation of the layers and extraction of the aqueous layer with Et_2O (2 x 20 mL), CH_2Cl_2 (2 x 20 mL), and EtOAc (2 x 20 mL). The

combined organic phase was dried with $MgSO_4$, filtered, and concentrated to give 5.30 g of a brown oil. Column chromatography (53 g silica gel, 15% ether/hexanes) yielded 3.10 g (78%) of a yellow oil, **16d**, as a mixture of diastereomers. ^1H nmr: ($CDCl_3$) δ 7.60 - 7.25 (m, 10 H), 5.90 - 4.50 (m, 1H), 3.80 - 3.60 (m, 8H), 2.90 - 1.90 (m, 3H), 1.20 - 1.00 (m, 3H); IR: ($CHCl_3$, cm^{-1}): 3059, 2993, 2952, 1732, 1548; HRMS: calculated for $C_{22}H_{25}NS_2O_6$ (M^+): 463.1123; found: 463.1126.

Amide ester 17: To a stirring solution of **16d** (1.50 g, 3.72 mmol, 1.00 eq), $NiCl_2 \cdot 6H_2O$ (8.84 g, 37.2 mmol, 10.0 eq), and methanol (35 mL) in a 250 mL, 3-neck round bottom flask cooled to 0°C was added $NaBH_4$ (4.22 g, 111.6 mmol, 30.0 eq) in portions over 30 min. The resultant black slurry was heated to reflux for 4 h. After cooling to room temperature, the mixture was filtered through Celite and concentrated to a light green slurry. To this was added $CHCl_3$ (30 mL) and brine (30 mL) and the mixture was shaken. After separating the layers, the aqueous layer was washed with $CHCl_3$ (3 x 20 mL) and EtOAc (3 x 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated to give 0.561 g of a pale yellow liquid. Column chromatography (6 g silica gel; solvent gradient: CH_2Cl_2 to 7% acetone/CH_2Cl_2) yielded 0.390 g (57%) of desired product, a colorless liquid, as a mixture of lactams. ^1H nmr: ($CDCl_3$) δ 5.85, 5.75 (br s, 1H), 3.70, 3.69 (s, 3H), 3.60 (m, 1H), 3.60 (m, 1H), 2.70 - 2.45 (m, 1H), 2.37 (m, 2H), 2.30 - 2.10 (m, 2H), 1.85 - 1.70 (m, 2H), 1.14 (dd, 1H), 1.05 (dd, 1H), 0.98 (dd, 1H); IR: ($CHCl_3$, cm^{-1}): 3229, 2957, 1736, 1691; HRMS: calculated for $C_9H_{15}NO_3$ (M^+): 185.1052; found: 185.1056.

1-Methyl-2,5-dioxo-pyrrolizidine (18): A mixture of **17** (234 mg, 1.26 mmol, 1.00 eq) in methanol (9 mL) and 0.5 N $NaOH_{(aq)}$ (2.46 mL, 1.23 mmol, 0.976 eq) was heated to 60°C overnight. After cooling, the mixture was treated with 10% $HCl_{(aq)}$ until pH = 1 was achieved. The mixture was concentrated in vacuo to produce a sticky, viscous residue which was dissolved in acetic anhydride (15 mL) and heated to 105°C overnight. Excess Ac_2O was removed by distillation at 90°C under aspirator vacuum. Toluene was added and removed by distillation. Toluene was added a second time and the distillation continued. The residue was taken to dryness in vacuo at room temperature. Column chromatography (4 g silica gel, 5% acetone/CH_2Cl_2) yielded 147 mg (76%, as a mixture of two diastereomers in 2.4:1 ratio) of desired product, **18**, as a white solid (mp : 74 - 76°C, recrystallized from cyclohexane). ^1H nmr: ($CDCl_3$) δ 4.49, 3.92 (ddd, 1H), 2.96 (dd, 1H), 2.80 - 2.50 (m, 3H), 2.29 (d, 1H), 2.00, 1.80 (m, 2H), 1.17, 1.04 (dd, 3H); IR: ($CHCl_3$, cm^{-1}): 2966, 1779, 1703; Analysis: calculated for $C_8H_{11}NO_2$: C, 62.74%; H, 7.19%; N, 9.15%; found: C, 62.53%; H, 7.21%; N, 9.07%.

1-Methyl-pyrrolizidine (19): Imide **18** (127.3 mg, 0.852 mmol) was treated with $LiAlH_4$ as described by Lukes and Janda.[26] After workup, ^1H nmr of the crude mixture using mesitylene as an internal standard indicated a yield of 81% of desired product **19** was achieved. A picrate salt was formed directly (mp: 230 - 242°C, literature mp: 229 - 239°C), the nmr spectrum of which was in agreement with that previously published.[29]

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