Tandem Ireland−Claisen Rearrangement Ring-Closing Alkene Metathesis in the Construction of Bicyclic β-Lactam Carboxylic Esters

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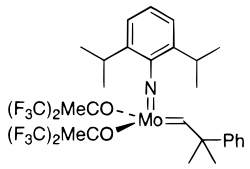
4-Alkenyl-2-azetidinone systems were converted to the corresponding ethyl 2-[4-alkenyl-2-oxo-1-azetidinyl]-4-pentenoates. In addition, 4-(2-propenyl-1-oxy)-, 4-(2-propenyl-1-thio)-, 4-[*N*-(2-propenyl)-(4-toluenesulfonyl)]- and (3*S*,4*R*)-4-(2-propenyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-azetidin-2-one were converted into β-lactam dienes via sequential *N*-alkylation, Ireland−Claisen ester enolate rearrangement and esterification. Ring-closing metathesis using the Schrock $[(CF_3)_2MeCO]_2$-Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$-2,6-*iso*-Pr$_2$) (**1**) or Grubbs Cl$_2$(Cy$_3$P)$_2$Ru=CHPh (**2**) carbenes gave a series of [5.2.0] and [6.2.0] bicycles. Subsequent elaboration of the analogous (2*R**,7*R*,8*S*)-*tert*-butyl 8-[(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-1-aza-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate (**15**), via selenation and desilylation, gave (+)-(2*S*,7*R*,8*S*)-*tert*-butyl 8-[(1*R*)-hydroxyethyl]-1-aza-9-oxobicyclo[5.2.0]-nona-2,4-diene-2-carboxylate (**18**), a novel type of bicyclic β-lactam. Diels−Alder cycloaddition further afforded tetracyclic systems exemplified by *tert*-butyl (1*R*,4*S*,5*R*,7*S*)-4-[(1*R*)-1-hydroxyethyl]-3,9,-11-trioxo-10-phenyl-2,8,10,12-tetraazatetracyclo[5.5.2.0.^{2,5}0^{8,12}]tetradec-13-ene-1-carboxylate (**19**).

The rapid espousal of ring-closing metathesis by synthetic organic chemists, following the introduction of well-defined molybdenum **1**[1] and ruthenium catalysts **2**,[2] is remarkable.[3,4] Such atom economic cyclization reactions



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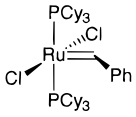

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have found application in the synthesis of carbocyclic, heterocyclic, and macrocyclic arrays.[5−10] Recently, we reported the use of ring-closing metathesis in the assembly of simple bicyclic β-lactams,[11] and extended the reaction to related enyne and dienyne β-lactam systems.[12] While these results clearly established that polyfunctional β-lactam dienes were excellent substrates for metathesis, the reactions were not appropriate for the synthesis of bioactive β-lactam carboxylic acids. For this metathetic approach to find utility in the generation of novel drug candidates, it is essential that it be capable of installing a carboxylic acid motif adjacent to the lactam nitrogen. Herein we disclose methods for incorporating the requisite framework via Ireland−Claisen rearrangement[13] and subsequent alkene metathesis. Such a strategy has recently been shown to be versatile for the synthesis of cyclohexenes, dihydropyrans, tetrahydropyridines, and related heterocycles.[14−16] Furthermore, we disclose a novel type of bicyclo[5.2.0]dienes, derived from the aforementioned systems, which was elaborated by Diels−Alder cycloaddition to tetracyclic β-lactam systems.

Results and Discussion

From our previous work in this field,[12] and in view of their ready accessibility from commercially available precursors, β-lactams **3a**−**c** were chosen. Reaction with ethyl glyoxalate followed by acetylation gave the corresponding acetates **5a**−**c**, which underwent smooth *C*-allylation with allyltrimethylsilane and boron trifluoride etherate to give dienes **6a**−**c** as approximately 1:1 mixtures of diastereoisomers (Scheme 1). Attempts to

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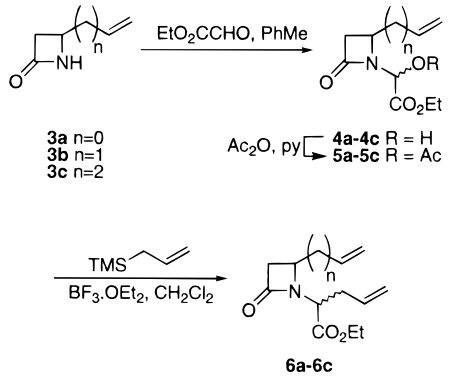
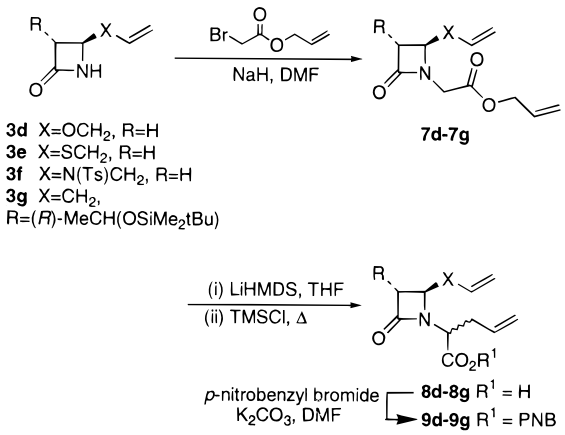
Scheme 1



Scheme 2



extend the protocol to generate heteroatom 4-substituted lactams were unsuccessful. This is presumably due to competing endocyclic iminium ion formation. These problems were not alleviated by recourse to other Lewis acidic catalysts, including trimethylsilyl trifluoromethanesulfonate and titanium tetrachloride, nor by modifying the nature of the leaving group (*p*-nitrobenzoate, trifluoromethanesulfonate, methanesulfonate). Therefore, it was necessary to develop an alternative approach to avoid these limitations.

We considered that such dienes could alternatively be prepared via Ireland−Claisen rearrangement[13] of silyl ketene acetals derived from allyl esters **7d**−**g**. Thus, alkylation of β-lactams **3d**−**g** with allyl bromoacetate furnished the Ireland−Claisen precursors **7d**−**g** (Scheme 2). Much to our delight, following the conditions of Baldwin and co-workers[17] the corresponding silyl ketene acetals underwent smooth rearrangement affording the carboxylic acids **8d**−**g** in excellent yield. Gratifyingly, the reaction proved to be perfectly amenable to scale-up, the rearrangement reactions being conducted on up to a 20 g scale. As in the case of the allylation reactions, the carboxylic acids **8d**−**g** were formed as inseparable 1:1 mixtures of diastereoisomers.

Though these products presented no inherent functional group incompatibility issues in metathesis reactions mediated by catalyst **2**, carboxylic acids **8d**−**g** had only limited solubility in chloroform or dichloromethane, the optimal solvents for metathesis using carbenes **1** or **2**, and were directly converted into the corresponding

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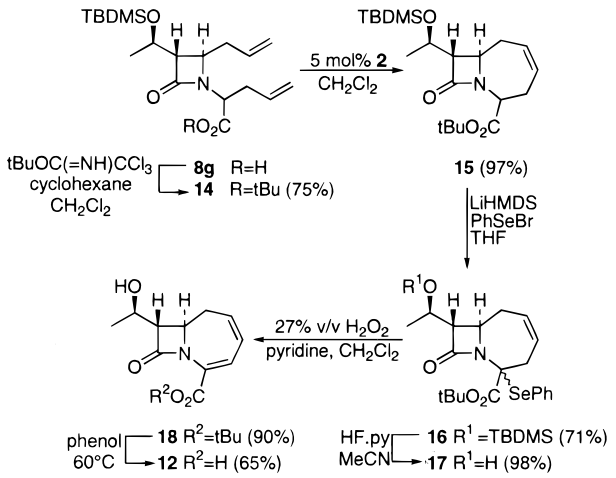
Table 1. Ring-Closing Metathesis of Dienes 6a−c, 9d−g

Entry[a]	Substrate	Product	%Yield[b]
1	**6a**	**10a**	0
2	**6b**	**10b**	92
3	**6c**	**10c**	76
4	**9d**	**10d**	98
5[c]	**9e**	**10e**	50 (85)[d]
6	**9f**	**10f**	86[e]
7	**9g**	**10g**	100[e,f]

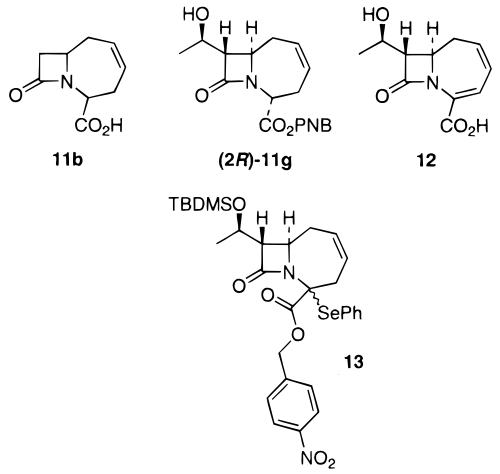
[a] All reactions performed in CH_2Cl_2 (0.05 M) under nitrogen for 12 h with 20 mol % ruthenium carbene **2** unless otherwise stated. [b] Combined yield of separated chromatographed diastereoisomers. [c] 5 mol % molybdenum carbene **1** employed. [d] Figure in parentheses denotes isolated yield after further addition of 5 mol % molybdenum carbene **1**. [e] Inseparable mixture of diastereoisomers. [f] All substrate consumed within 1 h.

p-nitrobenzyl esters **9d**−**g**. Attempted ring-closing metathesis of vinyl azetidinone **6a** (Table 1, entry 1) failed to provide any ring-closed adducts, as expected on the basis of previous investigations.[12] However, both diastereoisomers of dienes **6b** and **9g** underwent clean ring-closing metathesis in the presence of the ruthenium carbene **2** to provide the homocarbacephems **10b** and **10g** in excellent yields (entries 2, 7). Eight-membered ring closures leading to β-lactams **10d** and **10f** proceeded equally smoothly in the presence of catalyst **2** (entries 4, 6). The two diastereoisomers of diene **6c** were found to cyclize at substantially different rates, giving β-lactams **10c** as a 2:1 mixture of diastereoisomers. This rate difference is thought to arise from the relative orientation of the ester functionality in the diastereoisomeric transition states leading to the ring-closed adducts.[12] Treatment of thiadiene **9e** with the ruthenium carbene **2** resulted in immediate catalyst decomposition; however, the use of the molybdenum carbene **1** (5 mol %) resulted in rapid cyclization (2 h) to provide thioalkene **10e** as a single diastereoisomer. The remaining uncyclized diastereoisomer **9e** underwent slow metathesis (24 h) with additional molybdenum carbene **1** (5 mol %). The relative positions in the ^{1}H NMR spectra of the protons α to the ester, in concert with X-ray crystallography of desilylated (2*R*)-**11g**, provided the necessary information for the assignment of their structures. The utility of the above method for the preparation of compounds with potential biological activity was demonstrated by the saponification of ester **10b** to provide the bicyclic β-lactam carboxylic acid **11b** in 72% yield.

Scheme 3



We also had occasion to investigate the synthesis of [5.2.0] bicyclic diene systems, exemplified by **12**. Thus, ester **10g** was allowed to react with LDA and phenylselenyl bromide in THF in an attempt to furnish **13**. The



yield of the corresponding selenide was disappointing (21%), possibly explained in part by the relatively high acidity of the benzylic protons giving rise to competitive deprotonation. A change in protecting-group strategy was required, and mindful of the probable instability of the desired conjugated diene in strongly acidic media, it was thought that the *tert*-butyl ester would satisfactorily address both of these issues (Scheme 3). To this end, acid **8g** was treated with *O-tert*-butyl trichloroacetimidate, following the method of Jackson and co-workers,[18] affording ester **14** in 72% yield. Ring-closing metathesis proceeded without incident to give β-lactam **15**, which was converted to selenide **16** by a modified protocol, in which LiHMDS was used as base.

Our previously raised concerns over the instability were in part assuaged by the decision to elaborate the diene as late as possible in the synthesis. Thus, the *tert*-butyldimethylsilyl group was removed, prior to oxidative elimination of the selenide, by the action of HF·pyridine in acetonitrile, furnishing selenide **17** in 98% yield. Elimination with hydrogen peroxide resulted in excellent

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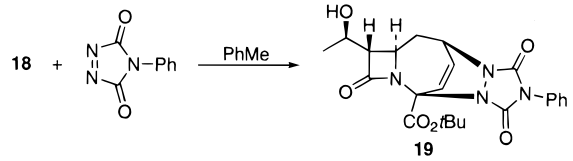
Scheme 4



conversion to diene **18**.[19] It was always our hope that the ester could be cleaved under the necessarily mild conditions required to maintain the integrity of the diene motif. Trifluoroacetic acid, although routinely used for such operations, was viewed to be unduly harsh in our circumstances, directing our attention to the procedure of Torii and co-workers,[20] who demonstrated the removal of β-lactam *tert*-butyl esters by using neat phenol. This cleavage is believed to be mediated by proton relay through a hydrogen-bonded phenolic matrix. This was indeed found to be a suitable method in this case, although it was observed that, on larger scale, the rate of reaction could be significantly increased by the addition of trace amounts of trifluoroacetic acid, without significantly deleterious effect, acid **12** being obtained in 65% yield.

With a route to such endocyclic dienes established, it seemed wise to probe their suitability in Diels−Alder reactions (Scheme 4). To this end, ester **18** was allowed to react with 4-phenyl-1,2,4-triazoline-3,5-dione, affording the cycloadduct **19** in high diastereoselectivity (*endo*:*exo* > 20:1).

In conclusion, we have demonstrated the facile assembly of bicyclic β-lactam carboxylic esters and hence carboxylic acids via tandem Ireland−Claisen rearrangement and subsequent alkene metathesis. It is clear that this strategy represents a powerful and rapid entry into novel pharmacologically interesting compounds.

Experimental Section

General. All reactions, except those using molybdenum catalyst **1**, were run in oven-dried glassware under a nitrogen atmosphere. Reactions using molybdenum catalyst **1** were performed in a glovebox under an argon atmosphere. THF and Et_2O were distilled from K/Ph_2CO and $Na/K/Ph_2CO$, respectively. CH_2Cl_2, DMF, and NEt_3 were distilled from CaH_2.

Chromatographed refers to column chromatography performed on BDH silica gel 60, 230−400 mesh ASTM. Concentrated refers to concentrated in vacuo. Analytical thin-layer chromatography (TLC) was performed on precoated glass backed plates (Merck Kieselgel 60 F_{254}) and visualized with ultraviolet light (254 nm) or potassium permanganate or vanillin as appropriate.

Molybdenum carbene **1** was prepared in-house,[1] ruthenium carbene **2** was purchased from Fluka, and (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one was kindly donated by GlaxoWellcome. 4-Ethenylazetidin-2-one (**3a**),[21] 4-(2-propenyl)azetidin-2-one (**3b**),[22] 4-(3-butenyl)azetidin-2-one (**3c**),[22] 4-(2-propenyl-1-oxy)azetidin-2-one (**3d**),[23] 4-(2-propenyl-1-thio)azetidin-2-one (**3e**),[12] 4-[*N*-(2-propenyl)-(4-toluenesulfonamido)]azetidin-2-one (**3f**),[24] (3*S*,4*R*)-4-(2-propenyl)-3-[(1*S*)-1-hydroxyethyl]azetidin-2-one (**3g**),[25] and ethyl 2-[4-(2-

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propenyl)-2-oxo-1-azetidinyl]-2-hydroxyacetate (**4b**)[12] allyl bromoacetate[26] were synthesized according to literature procedure with minor modifications where necessary.

General Procedure for the Preparation of Lactams 4a−4c. The following procedure is representative:

(2*R)-Ethyl 2-[(4*S**)-4-Ethenyl-2-oxo-1-azetidinyl]-2-hydroxyacetate and (2*S**)-Ethyl 2-[(4*S**)-4-Ethenyl-2-oxo-1-azetidinyl]-2-hydroxyacetate (4a)**. 4-Ethenylazetidin-2-one (0.155 g, 1.6 mmol, 1.0 equiv) was added to ethyl glyoxalate (50% in PhMe; 0.35 mL, 1.8 mmol) in PhMe (6 mL), and the solution was heated to reflux for 1 h. Ethyl glyoxalate (50% in PhMe; 0.18 mL, 0.88 mmol) was added and the solution heated to reflux for a further 15 h. The solution was allowed to cool and was concentrated and chromatographed (3:2 Et_2O:hexanes) to give **4a** as a mixture of diastereoisomers as a colorless oil (0.25 g, 79%): $R_f = 0.39$ (Et_2O); IR (thin film) 3401, 1747 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (m, 0.5H), 5.72 (m, 0.5H), 5.41−5.15 (m, 3H), 4.26 (m, 4H), 3.19 (dd, 0.5H, J = 5.6, 15.2 Hz), 3.19 (dd, 0.5H, J = 5.4, 15.1 Hz), 2.74 (m, 1H), 1.30 (t, 1.5H, J = 7.1 Hz), 1.28 (t, 1.5H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.5, 167.1, 166.4, 136.1, 135.5, 120.0, 119.6, 72.1, 71.1, 62.9, 62.7, 53.4, 52.0, 44.1, 14.1, 13.9; MS(CI) *m/e* 416 $(2M + NH_4)^+$, 399 $(2M + H)^+$, 217 $(M + NH_4)^+$, 200 $(M + H)^+$, 115, 73; HRMS(CI) calcd for $C_9H_{14}NO_4$ $(M + H)^+$ 200.0923, found 200.0925. Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.27; H, 6.58; N, 6.96.

General Procedure for the Preparation of Acetates 5a−5c. The following procedure is representative:[27]

(2*R)-Ethyl 2-Acetoxy-2-[(4*S**)-2-ethenyl-2-oxo-1-azetidinyl]acetate and (2*S**)-Ethyl 2-Acetoxy-2-[(4*S**)-2-ethenyl-2-oxo-1-azetidinyl]acetate (5a)**. Acetate **4a** (0.40 g, 2.0 mmol, 1.0 equiv) was added to Ac_2O (2.8 mL) in pyridine (2 mL), and the solution was stirred at room temperature for 10 h. The solution was diluted with Et_2O and washed with saturated $CuSO_4$ solution. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed (3:2 Et_2O:hexanes) to give **5a** as a mixture of diastereoisomers (0.35 g, 73%) as a viscous liquid: $R_f = 0.61$ (5:1 Et_2O:hexanes); IR (thin film) 1780, 1759 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 0.5H), 6.14 (s, 0.5H), 5.88 (m, 0.5H), 5.75 (m, 0.5H), 5.33 (m, 2H), 4.32−4.14 (m, 3H), 3.28 (dd, 0.5H, J = 5.7, 15.4 Hz), 3.25 (dd, 0.5H, J = 5.4, 15.3 Hz), 2.81 (m, 1H), 2.141 (s, 1.5H), 2.136 (s, 1.5H), 1.30 (t, 1.5H, J = 7.2 Hz), 1.28 (t, 1.5H J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.4, 166.7, 166.1, 164.32, 164.26, 135.6, 135.1, 120.2, 119.9, 72.00, 71.98, 62.6, 62.3, 54.3, 53.7, 44.8, 44.4, 20.6, 20.5, 14.0, 13.9; MS(CI) *m/e* 259 $(M + NH_4)^+$, 242 $(M + H)^+$, 210, 199, 140, 115, 102; HRMS(CI) calcd for $C_{11}H_{16}NO_5$ $(M + H)^+$ 242.1028, found 242.1035. Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 55.04; H, 6.38; N, 5.56.

General Procedure for the Preparation of Dienes 6a−6c. The following procedure is representative:

(2*R)-Ethyl 2-[(4*S**)-4-Ethenyl-2-oxo-1-azetidinyl]-4-pentenoate and (2*S**)-Ethyl 2-[(4*S**)-4-Ethenyl-2-oxo-1-azetidinyl]-4-pentenoate (6a)**. Allyltrimethylsilane (0.27 mL, 2.4 mmol, 5.0 equiv) was added to **5a** (0.115 g, 0.475 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL). The solution was cooled to 0 °C, and $BF_3{\cdot}OEt_2$ (0.21 mL, 1.7 mmol, 3.5 equiv) was added and the mixture allowed to warm to room temperature, at which point it was stirred for 16 h. The solution was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed (3:2 Et_2O:hexanes) to give **6a** as a mixture of diastereoisomers (71 mg, 67%) as a colorless oil: $R_f = 0.21$ (3:2 Et_2O:hexanes); IR (thin film) 1757, 1740 cm $^{-1}$; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.80 (m, 2H), 5.40−5.10 (m, 5H), 4.34 (m, 1H), 4.19 (q, 1H, J = 7.2 Hz), 4.17 (q, 1H, J = 7.2 Hz), 3.19 (dd, 0.5H, J = 5.3, 14.8 Hz), 3.15 (dd, 0.5H, J = 4.2, 15.2 Hz), 2.74−2.51 (m, 3H), 1.27 (t, 1.5H, J = 7.2 Hz), 1.26 (t, 1.5H, J = 7.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.0, 169.9, 167.3, 167.0, 137.5, 136.8, 133.6, 133.3, 119.3, 118.4, 118.3, 61.55, 61.49, 54.8, 54.6, 53.9, 43.6, 43.5, 34.3, 33.2, 14.22, 14.18; MS(CI) *m/e* 224 $(M + H)^+$, 168, 156, 124, 120, 78, 73, 61, 44; HRMS(CI) calcd for $C_{12}H_{18}NO_3$ $(M + H)^+$ 224.1287, found 224.1280. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.43; H, 7.65; N, 6.15.

General Procedure for the Preparation of Lactams 7d−7g. The following procedure is representative:

2-Propenyl 2-[2-Oxo-4-(2-propenyl-1-oxy)-1-azetidinyl]-acetate (7d). Sodium hydride (60% mineral oil dispersion, 160 mg, 4.00 mmol, 1.1 equiv) was added to **3d** (462 mg, 3.64 mmol, 1.0 equiv) in DMF (30 mL) at 0 °C. The mixture was stirred for 2 min, prior to the addition of allyl bromoacetate (0.87 mL, 7.3 mmol, 2.0 equiv). The mixture was allowed to warm to room temperature and was stirred for 2 h, after which time the reaction was diluted with Et_2O and quenched with H_2O. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. Chromatography (2:3 Et_2O:hexanes) afforded **7d** as a colorless oil (680 mg, 83%): $R_f = 0.18$ (3:2 Et_2O:hexanes); IR (thin film) 1771, 1747 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (m, 2H), 5.31 (m, 5H), 4.67 (d, 2H, J = 6.7 Hz), 4.11 (d, 2H, J = 4.9 Hz), 3.80 (d, 1H, J = 17.8 Hz), 3.18 (dd, 1H, J = 3.5, 15.3 Hz), 2.94 (app d, 1H, J = 15.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 166.1, 133.7, 131.3, 119.2, 117.8, 81.7, 68.9, 66.1, 45.0, 41.4; MS(CI) *m/e* 243 $(M + NH_4)^+$, 226 $(M + H)^+$, 185; HRMS(CI) calcd for $C_{11}H_{16}NO_4$ $(M + H)^+$ 226.1079, found 226.1082. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.72; H, 6.72; N, 6.31.

General procedure for the preparation of lactams 8d−8g. The following procedure is representative:

(2*R)-2-[(4*R**)-2-Oxo-4-(2-propenyl-1-oxy)-1-azetidinyl]-4-pentenoic acid and (2*S**)-2-[(4*R**)-2-Oxo-4-(2-propenyl-1-oxy)-1-azetidinyl]-4-pentenoic acid (8d)**. A freshly prepared solution of lithium hexamethyldisilazide in THF (2.0 mL, 0.93 mmol, 1.0 equiv) was added to **7d** (210 mg, 0.93 mmol, 1.0 equiv) in THF (4 mL) at −78 °C over 10 min. The mixture was stirred for a further 15 min, prior to the addition of Me_3SiCl (0.118 mL, 0.93 mmol, 1.0 equiv). The solution was heated at reflux for 4 h and cooled to 0 °C. MeOH (10 mL) was added dropwise over 10 min and the resultant solution was evaporated to dryness to give **8d** as an off-white paste (200 mg, 95%), which was used without further purification: $R_f = 0.10$ (1:4 MeOH: $CHCl_3$); IR (thin film) 3455, 1743, 1625 cm $^{-1}$; MS(CI) *m/e* 243 $(M + NH_4)^+$, 226 $(M + H)^+$, 185, 114, 92, 73, 59; HRMS(CI) calcd for $C_{11}H_{16}NO_4$ $(M + H)^+$ 226.1079, found 226.1089.

General Procedure for the Preparation of 4-Nitrobenzyl Esters 9d−9g. The following procedure is representative:

(2*R)-4-Nitrobenzyl 2-[(4*R**)-2-Oxo-4-(2-propenyl-1-oxy)-1-azetidinyl]-4-pentenoate and (2*S**)-4-Nitrobenzyl 2-[(4*R**)-2-Oxo-4-(2-propenyl-1-oxy)-1-azetidinyl]-4-pentenoate (9d)**. K_2CO_3 (81 mg, 0.59 mmol, 1.5 equiv), *p*-nitrobenzyl bromide (169 mg, 0.782 mmol, 2.0 equiv) and ^{n}Bu$_4$I (cat.) were added to **8d** (88 mg, 0.39 mmol, 1.0 equiv) in DMF (4 mL). The mixture was stirred for 12 h, prior to dilution with Et_2O and H_2O. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. Chromatography (1:4 Et_2O:hexanes) gave **9d** (120 mg, 85%) as a colorless oil: $R_f = 0.72$ (Et_2O); IR (thin film) 1767, 1747, 1523 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (m, 2H), 7.51 (dd, 2H, J = 2.1, 8.9 Hz), 5.83 (m, 2H), 5.32−5.08 (m, 7H), 4.43 (dd, 0.5H, J = 6.9, 8.1 Hz), 4.31 (dd, 0.5H, J = 6.7, 8.8 Hz), 4.03 (m, 1H), 3.07 (dd, 0.5H, J = 3.7, 6.0 Hz), 3.02 (dd, 0.5H, J = 3.9, 6.0 Hz), 2.90 (t, 0.5H, J = 1.9 Hz), 2.84 (t, 0.5H, J = 1.9 Hz), 2.71 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.8, 166.5, 142.7, 134.0, 133.9, 133.4, 133.1, 129.0, 128.8, 127.4, 124.3, 124.2, 124.1, 119.4, 119.1, 118.1, 117.9, 82.3, 81.2, 68.7, 66.2, 66.1,

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(27) During these investigations an alternative esterification procedure was disclosed and employed, with comparable results: Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342−2347.

54.6, 54.5, 45.1, 44.7, 35.2, 33.5; MS(CI) *m/e* 378 $(M + NH_4)^+$, 361 $(M + H)^+$, 320, 303, 261, 243, 226, 122; HRMS(CI) calcd for $C_{18}H_{21}N_2O_6$ $(M + H)^+$ 361.1400, found 361.1396.

General Procedure for the Ring-Closing Metathesis of Dienes 10b−10g. Carbene **1** or **2** was added to the corresponding diene (30−50 mg) in CH_2Cl_2 (2 mL) (Table 1). The mixture was allowed to stir for 12 h prior to destruction of the catalyst by exposure to air. The mixture was evaporated and chromatographed.

(2*R,7*R**)-Ethyl 1-Aza-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate and (2*S**,7*R**)-Ethyl 1-Aza-9-oxobicyclo[5.2.0]-non-4-ene-2-carboxylate (10b):** Separable diastereoisomers both as colorless oils (combined yield 92%): (2*R**,7*R**)-**10b**: $R_f = 0.41$ (Et_2O); IR (thin film) 1742 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.83 (m, 1H), 4.63 (t, 1H, $J = 4.4$ Hz), 4.19 (m, 2H), 3.90 (m, 1H), 3.11 (dd, 1H, $J = 4.8$, 14.6 Hz), 2.67 (m, 3H), 2.49 (dd, 1H, $J = 3.1$, 7.8, 15.8 Hz), 2.40 (m, 1H), 1.27 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.8, 131.1, 128.7, 61.4, 51.1, 49.1, 43.2, 33.5, 30.0, 14.2; MS(CI) *m/e* 227 $(M + NH_4)^+$, 210 $(M + H)^+$, 136; HRMS(CI) calcd for $C_{11}H_{16}NO_3$ $(M + H)^+$ 210.1130, found 210.1126. (2*S**,7*R**)-**10b**: $R_f = 0.10$ (Et_2O); IR (thin film) 1742 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (m, 1H), 5.57 (m, 1H), 4.41 (t, 1H, $J = 4.0$ Hz), 4.20 (2H, q, $J = 7.1$ Hz), 4.05 (m, 1H), 3.05 (dd, 1H, $J = 4.7$, 14.6 Hz), 2.75−2.44 (m, 5H), 1.25 (t, 3H $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 165.7, 130.3, 124.7, 61.5, 55.1, 50.2, 41.8, 35.3, 27.1, 14.1; MS(CI) *m/e* 436 $(2M + NH_4)^+$, 419 $(2M + H)^+$, 227 $(M + NH_4)^+$, 210 $(M + H)^+$, 168, 136, 94; HRMS(CI) calcd for $C_{11}H_{16}NO_3$ $(M + H)^+$ 210.1130, found 210.1132.

(2*R,7*R**)-1-Aza-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylic Acid (11b).** Aqueous NaOH (0.25M; 1.34 mL, 0.33 mmol, 1.2 equiv) was added dropwise to (2*R**, 7*R**)-**10b** (58.3 mg, 0.279 mmol, 1.0 equiv) in THF (2.5 mL) at 0 °C. The mixture was stirred for 0.5 h, diluted with saturated aqueous NaCl and CH_2Cl_2, and acidified to pH 2. The organic layer was separated, and the aqueous solution was twice extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated to dryness. Chromatography (1:4 MeOH:$CHCl_3$) yielded **11b** (37 mg, 72%): $R_f = 0.18$ (1:4 MeOH:$CHCl_3$); IR (thin film) 3485, 1730 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (m, 1H), 5.87 (m, 1H), 4.56 (t, $J = 4.6$ Hz), 3.88 (m, 1H), 3.06 (dd, 1H, $J = 4.7$, 14.7 Hz), 2.67 (m, 3H), 2.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 168.6, 132.2, 130.0, 52.7, 50.8, 43.3, 34.0, 30.5; MS(CI) *m/e* 199 $(M + NH_4)^+$, 182 $(M + H)^+$, 61, 44; HRMS(CI) calcd for $C_9H_{12}NO_3$ $(M + H)^+$ 182.0817, found 182.0819.

(+)-(2*R*,7*R*,8*S*)-4-Nitrobenzyl 1-Aza-8-[(1*R*)-hydroxyethyl]-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate and (−)-(2*S*,7*R*,8*S*)-4-Nitrobenzyl 1-Aza-8-[(1*R*)-hydroxyethyl]-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate (11g). *N*,*N*′-Diisopropylethylamine trihydrofluoride (49.8 mg, 0.263 mmol, 1.25 equiv) was added to **10g** (100 mg, 0.211 mmol, 1.0 equiv) in *N*-methyl-2-pyrrolidinone (0.2 mL). The mixture was stirred at room temperature for 4 d, at which point saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with saturated NaCl, dried ($MgSO_4$), and evaporated to dryness. Chromatography (Et_2O) yielded separable diastereoisomers of **11g** (59 mg, 77%): (2*R*)-**11g**: $R_f = 0.20$ (Et_2O); $[\alpha]^{19}_D = +84.0$ (*c* 0.50, $CHCl_3$); IR (thin film) 3447, 1737, 1522 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (m, 2H), 7.52 (d, 2H, $J = 8.7$ Hz), 5.94 (m, 1H), 5.77 (m, 1H), 5.25 (s, 2H), 4.72 (t, 1H, $J = 4.5$ Hz), 4.16 (m, 1H), 3.87 (m, 1H), 2.91 (dd, 1H, $J = 2.0$, 6.0 Hz), 2.68 (m, 2H), 2.48 (m, 2H), 1.83 (broad s, 1H), 1.30 (d, 3H, $J = 6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.3, 147.8, 142.4, 131.5, 128.5, 128.2, 123.9, 65.6, 65.4, 63.6, 52.4, 51.0, 33.1, 29.7, 21.5; MS(CI) *m/e* 378 $(M + NH_4)^+$, 361 $(M + H)^+$, 156, 124, 61; HRMS(CI) calcd for $C_{18}H_{21}N_2O_6$ $(M + H)^+$ 361.1400, found 361.1413. *Crystal data for* (2*R*)-**11g**: $C_{18}H_{20}N_2O_6$, $M = 360.4$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 7.240(1)$ Å, $b = 8.937(2)$ Å, $c = 27.838(2)$ Å, $V = 1801.2(2)$ Å^3, $Z = 4$, $D_c = 1.329$ g cm^{-3}, μ(Cu Kα) = 8.44 cm^{-1}, $F(000) = 760$, $T = 293$ K; clear blocks, 1.00 × 1.00 × 1.00 mm, Siemens P4/PC diffractometer, ω-scans, 1765 independent reflections. The structure was solved by direct methods, and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give $R_1 = 0.043$, $wR_2 = 0.114$ for 1619 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 128°$] and 240 parameters. The assignment of the absolute chirality of the 2 center as *R* was by internal reference to the already known 1*R*, 7*R*, and 8*S* centers. (2*S*)-**11g**: $R_f = 0.10$ (Et_2O); $[\alpha]^{19}_D = -2.6$ (*c* 0.50, $CHCl_3$); IR (thin film) 3432, 1738, 1522 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 2H, $J = 8.6$ Hz), 7.50 (d, 2H, $J = 8.4$ Hz), 5.65 (m, 1H), 5.55 (m, 1H), 5.31 (d, 1H, $J = 13.3$ Hz), 5.21 (d, 1H, $J = 13.3$ Hz), 4.54 (t, 1H, $J = 4.0$ Hz), 4.24 (m, 1H), 4.12 (m, 1H), 2.88 (dd, 1H, $J = 2.0$, 5.4 Hz), 2.76 (m, 2H), 2.49 (m, 2H), 1.81 (broad s, 1H), 1.30 (d, 3H, $J = 6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 166.2, 147.8, 142.6, 130.5, 128.4, 124.6, 123.8, 65.8, 64.8, 62.3, 54.9, 53.1, 35.0, 26.9, 21.5; MS(CI) *m/e* 378 $(M + NH_4)^+$, 361 $(M + H)^+$, 277, 257, 240; HRMS(CI) calcd for $C_{18}H_{21}N_2O_6$ $(M + H)^+$ 361.1400, found 361.1396.

The crystallographic data for (2*R*)-**11g** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-143691. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB12 1EZ, U.K. (Fax: 44+-(1223)336-033. E-mail: teched@chemcrys.cam.ac.uk.)

(2*R*)-*tert*-Butyl 2-{(3*S*,4*R*)-3-[(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-(2-propenyl)-1-azetidinyl}-4-pentenoate and (2*S*)-*tert*-Butyl 2-{(3*S*,4*R*)-3-[(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-(2-propenyl)-1-azetidinyl}-4-pentenoate (14). A solution of *O*-*tert*-butyl trichloroacetimidate (0.63 mL, 3.6 mmol, 2.0 equiv) in cyclohexane (3 mL) was added to **8g** (652 mg, 1.77 mmol, 1.0 equiv) in CH_2Cl_2 (2.2 mL). $BF_3{\cdot}OEt_2$ (35 μL) was then added, and the mixture was stirred at room temperature for 6 h. Solid $NaHCO_3$ (500 mg) was added prior to filtration of the mixture through a short plug of silica. Evaporation to dryness gave **14** as a colorless oil as a mixture of inseparable diastereoisomers (554 mg, 75%): $R_f = 0.53$ (60:40 Et_2O:hexanes); IR (thin film) 1758, 1737 cm $^{-1}$; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.77 (m, 2H), 5.12 (m, 4H), 4.20 (m, 1H), 4.08 (m, 1H), 3.85 (m, 0.5H), 3.65 (m, 0.5H), 2.76 (dd, 0.5H, $J = 2.1$, 6.8 Hz), 2.74 (dd, 0.5H, $J = 2.3$, 6.1 Hz), 2.58 (m, 3H), 2.31 (m, 1H), 1.45 (s, 4.5H), 1.44 (s, 4.5H), 1.21 (d, 1.5H, $J = 6.7$ Hz), 1.18 (d, 1.5H, $J = 6.2$ Hz), 0.86 (s, 4.5H), 0.85 (s, 4.5H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (67.5, $CDCl_3$) δ 168.9, 168.4, 167.5, 167.3, 133.7, 133.6, 117.9, 81.9, 81.8, 66.5, 66.0, 62.3, 56.0, 55.2, 54.9, 38.2, 38.0, 36.2, 33.6, 27.91, 27.86, 26.1, 25.7, 22.8, 17.8, −4.5, −4.8; MS(CI) *m/e* 424 $(M + H)^+$, 366, 310, 282, 159, 95, 73, 57, 41; HRMS(CI) calcd for $C_{23}H_{42}NO_4Si$ $(M + H)^+$ 424.2883, found 424.2879.

(2*R*,7*R*,8*S*)-*tert*-Butyl 1-Aza-8-[(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate and (2*S*,7*R*,8*S*)-*tert*-Butyl 1-Aza-8-[(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-9-oxobicyclo[5.2.0]non-4-ene-2-carboxylate (15): from **14** following the general procedure for ring-closing metathesis; colorless oil as a mixture of inseparable diastereoisomers (97%): $R_f = 0.41$ (3:2 Et_2O:hexanes); IR (thin film) 1757 cm $^{-1}$; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.98−5.58 (m, 2H), 4.50 (t, 0.5H, $J = 4.3$ Hz), 4.27 (t, 0.5H, $J = 3.9$ Hz), 4.22−4.03 (m, 1H), 3.80 (1H, dq, $J = 2.1$, 9.9 Hz), 2.77 (dd, 0.5H, $J = 2.1$, 7.7 Hz), 2.75 (m, 0.5H), 2.64−2.38 (m, 4H), 1.43 (s, 4.5H), 1.42 (s, 4.5H), 1.25 (d, 1.5H, $J = 6.0$ Hz), 1.19 (d, 1.5H, $J = 6.2$ Hz), 0.86 (s, 4.5H), 0.85 (s, 4.5H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.0, 168.4, 166.0, 165.9, 130.9, 130.2, 128.4, 124.7, 81.5, 66.7, 64.9, 64.2, 62.4, 55.3, 53.1, 52.4, 51.0, 34.9, 32.9, 30.1, 27.9, 27.8, 27.0, 25.7, 25.6, 22.5, 22.4, 17.8, −4.2, −4.9, −5.2; MS(CI) *m/e* 396 $(M + H)^+$, 340, 282, 90, 73, 57; HRMS(CI) calcd for $C_{21}H_{38}NO_4Si$ $(M + H)^+$ 396.257, found 396.2571.

(2*R,7*R*,8*S*)- *tert*-Butyl 1-Aza-8-[(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-9-oxo-2-phenylselenylbicyclo[5.2.0]-non-4-ene-2-carboxylate (16).** A freshly prepared solution of LiHMDS (0.5 M in THF, 4.93 mL) was added to **15** (481 mg, 1,12 mmol, 1.0 equiv) in THF (11 mL) at −78 °C. The temperature was raised to −50 °C, maintained for 0.5 h, and lowered to −78 °C, at which time a solution of phenylselenyl bromide (580 mg, 2.46 mmol, 2.2 equiv) in THF (8 mL) was

added. The mixture was allowed to warm to room temperature and was quenched with saturated NH_4Cl. Et_2O was added to the solution, and the organic layer was dried ($MgSO_4$) and evaporated to dryness. Chromatography (1:4 Et_2O:hexanes) afforded **16** as a colorless oil as a mixture of inseparable diastereoisomers (451 mg, 71%): $R_f = 0.68$ (3:2 Et_2O:hexanes); IR (thin film) 1762, 1723, 1652 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.46−7.32 (m, 3H), 5.55 (m, 2H), 3.62 (ddd, 1H, J = 1.3, 4.8, 9.0 Hz), 3.52 (m, 1H), 3.01 (dt, 1H, J = 3.0, 16.1 Hz), 2.84 (dd, 1H, J = 8.6, 16.0 Hz), 2.55 (dd, 1H, J = 1.7, 8.2 Hz), 2.38 (broad s, 2H), 1.46 (s, 9H), 1.23 (d, 1H, J = 6.1 Hz), 0.86 (s, 9H), 0.03 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.1, 164.6, 138.9, 130.2, 129.6, 129.2, 128.8, 127.6, 124.7, 82.8, 67.5, 63.5, 62.8, 55.7, 36.5, 36.0, 27.8, 25.8, 25.6, 22.5, 17.9, −4.1, −4.6; MS(FAB) *m/e* 552 $(M + H)^+$, 338; HRMS(FAB) calcd for $C_{27}H_{42}NO_4SeSi$ $(M + H)^+$ 552.2050, found 552.2048. Anal. Calcd for $C_{27}H_{41}NO_4SeSi$: C, 58.89; H, 7.50; N, 2.54. Found: C, 58.92; H, 7.38; N, 2.48.

(2*R,7*R*,8*S*)-*tert*-Butyl 1-Aza-8-[(1*R*)-hydroxyethyl]-9-oxo-2-phenylselenylbicyclo[5.2.0]non-4-ene-2-carboxylate (17).** An excess of HF·pyridine (150μL) was added to **16** (1.21 g, 2.15 mmol, 1.0 equiv) in MeCN (14 mL). The mixture was stirred for 3 h at room temperature prior to the addition of saturated $NaHCO_3$. The mixture was washed with EtOAc, and the combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Chromatography (4:1 Et_2O:hexanes) afforded **17** as a colorless oil (920 mg, 98%): $R_f = 0.31$ (Et_2O); IR (thin film) 1746, 1652 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.56 (m, 3H), 5.56 (m, 2H), 3.84 (ddd, 1H, J = 1.7, 4.9, 10.0 Hz), 3.74 (m, 1H), 3.03 (dt, 1H, J = 2.6, 16.2 Hz), 2.88 (dd, 1H, J = 8.2, 16.2 Hz), 2.61 (dd, 1H, J = 7.0, 6.6 Hz), 2.47 (m, 2H), 1.64 (broad s, 1H), 1.46 (s, 9H), 1.24 (d, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 164.9, 138.7, 130.0, 129.6, 128.8, 124.7, 82.9, 65.81, 65.76, 63.6, 62.2, 54.8, 36.6, 35.9, 27.8, 21.5, 15.2; MS(FAB) *m/e* 438 $(M + H)^+$, 394, 338, 224; HRMS(FAB) calcd for $C_{21}H_{28}NO_4Se$ $(M + H)^+$ 438.1184, found 438.1184.

(+)-(7*R*,8*S*)-*tert*-Butyl 1-Aza-8-[(1*R*)-hydroxyethyl]-9-oxobicyclo[5.2.0]nona-2,4-diene-2-carboxylate (18). Pyridine (0.34 mL, 4.2 mmol, 2.0 equiv) was added to **17** (0.92 g, 2.1 mmol, 1.0 equiv) in CH_2Cl_2 (22 mL). The solution was cooled to −78 °C, and aqueous hydrogen peroxide (20%v/v, 5.88 M; 1.8 mL) was added. After the mixture was allowed to warm to room temperature over 2 h, the reaction was diluted with Et_2O, washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. Chromatography (1:4 Et_2O:hexanes) yielded **18** as a pale yellow oil (556 mg, 90%): $R_f = 0.26$ (Et_2O); $[\alpha]^{19}_D = +266.0$ (*c* 1.00, $CHCl_3$); IR (thin film) 3448, 1744 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (m, 3H), 4.34 (m, 1H), 3.57 (dt, 1H, J = 2.3, 8.9 Hz), 2.96 (ddd, 1H, J = 2.3, 7.9, 15.7 Hz), 2.81 (dd, 1H, J = 2.6, 5.8 Hz), 2.53 (ddt, 1H, J = 3.0, 8.9, 20.5 Hz), 1.80 (broad s, 1H), 1.53 (s, 9H), 1.37 (d, 3H, J = 6.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 164.2, 162.2, 134.5, 129.9, 123.8, 116.1, 82.4, 65.3, 50.5, 37.6, 27.9, 21.6, 15.3; MS(FAB) *m/e* 280 $(M + H)^+$, 240, 224, 120; HRMS(FAB) calcd for $C_{15}H_{22}NO_4$ $(M + H)^+$ 280.1544, found 280.1549.

(+)-(7*R*,8*S*)-1-Aza-8-[(1*R*)-hydroxyethyl]-9-oxobicyclo-[5.2.0]non-2,4-diene-2-carboxylic Acid (12). Phenol (350 mg) was added to **18** (35 mg, 0.12 mmol, 1.0 equiv) and the mixture was heated to 40 °C, melting the phenol, at which point TFA (1μL) was added. The mixture was heated at 60 °C for 6 h. After cooling to room temperature, the phenol was removed by vacuum sublimation (∼0.5 mbar). Chromatography (1:4 MeOH:$CHCl_3$) afforded **12** (17 mg, 65%): $R_f = 0.20$ (1:4 MeOH: $CHCl_3$); $[\alpha]^{18}_D = +95.4$ (*c* 0.70, MeOH); IR (thin film) 3373, 1727, 1636, 1574 cm $^{-1}$; ^{1}H NMR (400 MHz, CD_3OD) δ 6.38 (d, 1H, J = 8.3 Hz), 6.17 (m, 1H), 5.97 (m, 1H), 4.20 (m, 1H), 3.59 (m, 1H), 2.96 (ddd, 1H, J = 2.0, 8.2, 16.3 Hz), 2.81 (dd, 1H, J = 2.2, 6.1 Hz), 2.57 (tq, 1H, J = 2.9, 9.2, 10.4 Hz), 1.30 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 172.6, 168.3, 136.2, 133.7, 124.8, 118.4, 66.2, 64.3, 52.7, 38.1, 21.9.

***tert*-Butyl (1*R*,4*S*,5*R*,7*S*)-4-[(1*R*)-1-hydroxyethyl]-3,9,11-trioxo-10-phenyl-2,8,10,12-tetraazatetracyclo[5.5.2.0^{2,5}.0^{8,12}]-tetradec-13-ene-1-carboxylate (19).** 4-Phenyl-1,2,4-triazoline-3,5-dione (24.2 mg, 0.138 mmol, 1.5 equiv) was added to **18** (27 mg, 92 μmol, 1.0 equiv) in PhMe (2 mL). The mixture was stirred at room temperature for 6 h. Concentration to dryness and purification by column chromatography (Et_2O) gave **19** (36 mg, 83%): $R_f = 0.33$ (EtOAc); IR (thin film) 3373, 1727 cm $^{-1}$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (m, 5H), 6.75 (dd, 1H, J = 7.2, 9.0 Hz), 6.34 (1H, d, J = 8.8 Hz, 1H), 5.21 (m, 1H), 3.98 (m, 1H), 3.63 (m, 1H), 2.70 (dd, 1H, J = 1.8, 7.2 Hz), 2.54 (ddd, 1H, J = Hz), 2.20 (m, 1H), 1.56 (s, 9H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.2, 163.2, 151.9, 151.3, 132.5, 131.0, 130.1, 129.7, 128.7, 127.4, 86.2, 73.2, 66.9, 64.8, 51.7, 51.2, 37.9, 28.0, 21.9; MS(FAB) *m/e* 455 $(M + H)^+$, 399, 290, 176, 166, 152, 135, 120, 109, 97, 91, 83, 77, 69, 55; HRMS(FAB) calcd for $C_{23}H_{27}N_4O_6$ $(M + H)^+$ 455.1931, found 455.1926.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of **4c**, **9d**−**f**, **10b**−**g**, **11b**, **11g**, **12**, **14**−**15** and **17**−**19**, NOE measurements on **19**, and X-ray crystallographic data for (*2R*)-**11g** and full characterization data for **4b**, **5b** and **5c**, **6b** and **6c**, **7e**−**7g**, **8e**−**8g**, **9e**−**9g**, and **10c**−**10g**. This material is published free of charge via the Internet at http://pubs.acs.org.

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