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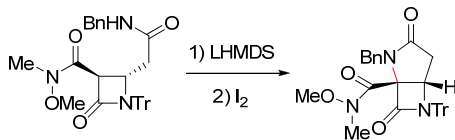
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Graphical Abstract



Preparation of fused β -lactams through Weinreb amide α -anions

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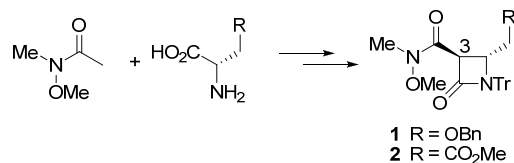
Abstract: Enantiomerically pure β -lactams bearing a Weinreb amide functionality at the C3 position have been shown to be excellent substrates for α -alkylation reactions, generating C3 quaternary centers with predictable absolute stereochemistry. In addition, oxidative coupling of C3/C4 dianions affords entry to fused β,γ -bisectam systems.

Introduction

Azetid-2-ones (β -lactams) are among the most highly investigated heterocyclic ring systems. Beyond the obvious impact on antibiotic research and treatment,¹ β -lactams have expressed biological activity in cholesterol absorption² and as a target of viral proteases.³ As synthetic organic reagents,^{4,5} β -lactams offer a well-defined stereochemical relationship between the adjacent sp^3 centers and an amide carbonyl that is reactive by virtue of the 4-membered ring strain. In peptide chemistry β -lactams have been employed as turn mimics^{6,7} and as precursors to β -amino acids^{8,9} and their related polymers¹⁰ (β -foldamers^{11,12}) that have been the focus of much study. New synthetic methods for the preparation of this ring system continue to appear in the literature with great frequency.^{13,14}

Recently, we presented a new route to enantiomerically pure (EP) β -lactams, such as **1** and **2**, from readily available α -amino acids in a process that is efficient both in the use of photochemistry for the key reaction and in the dearth of chromatographic separations (Scheme 1).¹⁵ In addition, the β -lactam Weinreb amide functionality is able to effectively undergo reactions with Grignard and alkyllithium reagents without opening of the β -lactam ring due to the steric presence of the N-Tr group. Herein we report our continuing studies on this β -lactam system, with the goal of articulating reaction pathways toward synthetic building blocks offering myriad (orthogonal) functionalities around the EP four-membered ring. The specific focus of the present studies was on functionalization of the C3 center. In particular, we have found that alkylation reactions occur with predictable stereochemistry at this activated carbon. In addition, we present our results on the oxidative coupling of the dianion formed

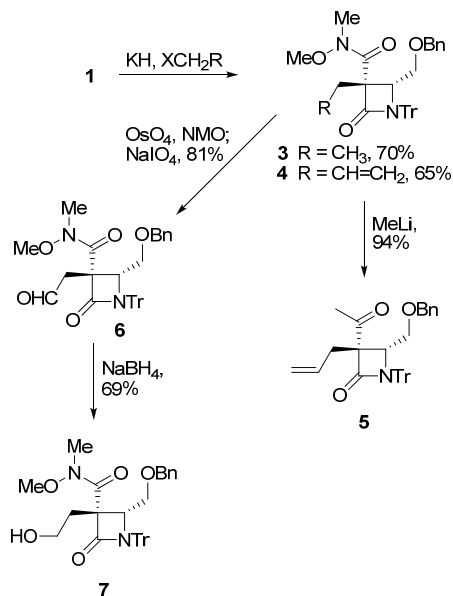
from deprotonation of the C3 position and a C4 pendant N-H amide functionality, resulting in the formation of a diazabicyclo[3.2.0]heptane structure.



Scheme 1. Previous Work

Results and Discussion

Generally, Weinreb amides have not been effective α -anion-stabilizing functionalities¹⁶; they are more often introduced into the molecule of interest and directly reacted with alkyllithium or Grignard reagents, or hydride reducing agents. Indeed, our published work documents this technology within the context of β -lactam **1**.¹⁵ Furthermore, our synthetic path to β -lactams involves the anion of commercial *N*-methoxy-*N*-methylacetamide reacting with an acylating agent that proceeds in excellent yield (*vide infra*). Given the generally modest results when standard strong bases have been employed for Weinreb amide α -deprotonation, we decided to employ KH, a base that we have used effectively in the past.¹⁷ In the event, alkylation of the anion of **1** with both EtI and allylbromide/NaI afforded the expected products **3** and **4**, respectively, in good yield (Scheme 2). The major product derived from approach of the electrophile from the least hindered face, opposite to the $-\text{CH}_2\text{OBn}$ group, as evidenced by a single crystal X-ray analysis of **4**.^{18,19}

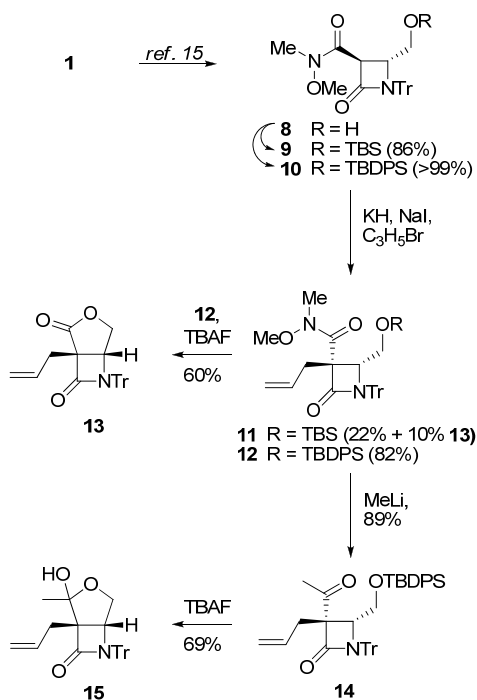


Scheme 2. α -Alkylation

Reduction of the Weinreb amide with MeLi proceeded in excellent yield in the presence of the adjacent quaternary center, affording methyl ketone **5**. Elaboration of the allyl functionality in **4** proceeded by

treatment with catalytic OsO₄ followed by NaIO₄ to provide the chain-shortened aldehyde **6**, which was reduced in good yield with NaBH₄ to afford the corresponding alcohol **7** (Scheme 2).

Our inability to remove the benzyl group in the presence of the allyl double bond in **4** necessitated a change in the C4 protection scheme (Scheme 3). We had published the standard deprotection of **1** to provide **8** previously,¹⁵ and introduction of both the –TBS and the –TBDPS group on the primary alcohol proceeded in excellent yield to give **9** (86%) and **10** (>99%), respectively. Allyl introduction employing the same methodology as found in Scheme 2 afforded vastly different yields, with **9** providing only 22% yield of the expected product **11** while **10** returned **12** in 82% as a single diastereomer. Deprotection of **12** with TBAF in refluxing THF afforded fused bicyclic lactone **13**, thereby confirming the *cis* relationship between the Weinreb amide and hydroxymethyl side chain. Compound **13** was also identified in the reaction mixture that produced **11**, suggesting instability of the –TBS group to the reaction conditions. Ketone production from **12** via methyllithium treatment proceeded without incident to deliver **14** and deprotection of the hydroxymethyl group again led to collapse of the alkoxide onto the *cis*-C3 carbonyl functionality with production of lactol **15**.



Scheme 3. Bicyclo[3.2.0] framework

Our success in accessing and reacting the β -lactam Weinreb amide α -anion, together with our ability to manipulate the C4 substituent, presented alternative possibilities for generating bicyclo[3.2.0] systems beyond compounds **13** and **15**. Our attention turned to diazabicyclo[3.2.0] heptane **16**, a ring system that was most recently described in the primary literature²⁰ as an alternative biologically active core structure to the corresponding β -lactone natural product proteasome inhibitors exemplified by salinosporamide A (Figure 1).

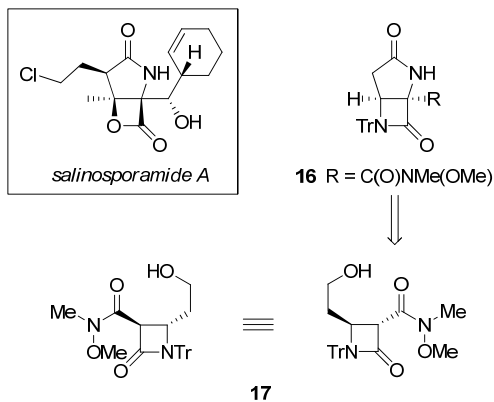
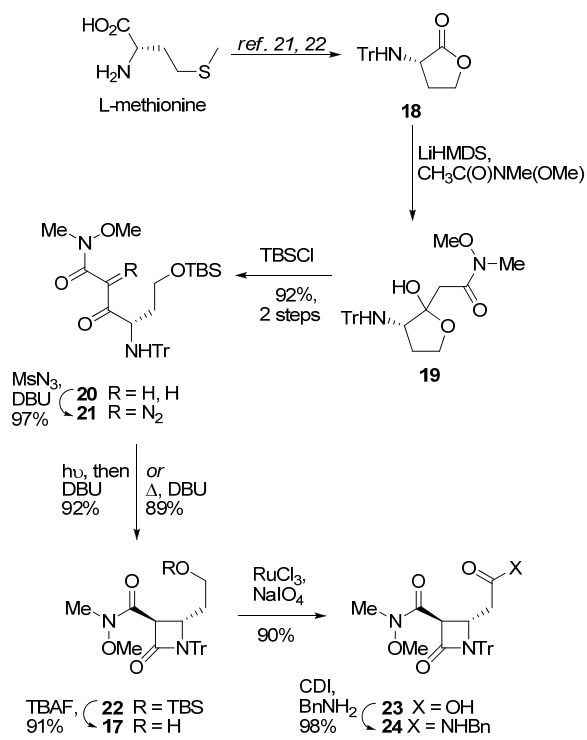


Figure 1. Diazabicyclo[3.2.0] retrosynthesis

In designing our approach to **16** we were also cognizant of one perceived shortcoming in our published work with β -lactam **2**. In that previous effort, both the C4 carbomethoxy and C3 Weinreb amide groups reacted competitively with methyllithium. While we were able to provide a satisfactory solution through selective lithium complexation of the Weinreb amide,¹⁵ it was decided to develop an alternative approach that would result in the production of a unique β -lactam with a reduced two-carbon substituent at C4, i.e., β -lactam **17**. Toward this end, L-methionine was subjected to van der Donk's protocol²¹, followed by trityl protection to provide known²² crystalline lactone **18** on multigram scale in 70% yield. Treatment of **18** with the anion of *N*-methyl-*N*-methoxyacetamide proceeded to give the corresponding lactol **19** (stereochemistry not defined). Protection of the primary alcohol functionality with TBSCl under standard conditions released the β -ketoamide functionality to give **20** in 92% yield for the two steps. Diazo transfer afforded **21** in 97% yield, ready for diazo decomposition, Wolff rearrangement and amine collapse onto the transiently formed ketene. This cascade of reactions was accomplished under both photolytic (4.5 h, 92%) and thermal (1 h, 89%) conditions, each providing excellent yield of the desired product **22**. Removal of the -TBS protection group led to free alcohol **17** in 91% yield. Oxidation to acid **23** and amide formation to give **24** proceeded without incident and in excellent yield (Scheme 4).

The key reaction for the formation of **16** was the oxidative coupling between the anion at C3 and the anion produced by deprotonation of the benzyl amide appended to C4 in **24**. While there are numerous examples of C-C bond formation through oxidative coupling,²³ fewer C-N bond forming events have been described.²⁴ Furthermore, we are unaware of the use of the α -anion of a Weinreb amide in this technology.

Table 1 provides our results to date. The use of hypervalent iodine compounds without preformation of the dianion species gave minimal desired product, and classic copper and iron complexes likewise led to poor results. Consistent, albeit modest, success came from treatment of the dianion of **24** with I₂. Treatment of the dianion with NBS also resulted in desired material.



Scheme 4. L-Met to β -lactam

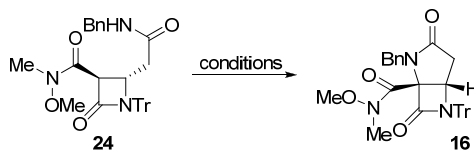


Table 1. Oxidative coupling of lactam dianion

Reagents	Conditions	Yield
PhI(OAc) ₂	CH ₃ CN, RT	NR
PhIO, TBAI	Toluene, RT	5%
1) LHMDS 2) PhI(OAc) ₂	THF, -78 to 0 °C	5%
1) LHMDS 2) I ₂	THF, -78 to 0 °C	32%
1) LHMDS 2) Cu(OAc) ₂	THF, -78 to 0 °C	NR
1) LHMDS 2) Fe(OAc) ₂	THF, -78 to 0 °C	NR
1) LHMDS 2) NBS	THF, -78 to 0 °C	28%

Conclusions

In conclusion, we have demonstrated that β -lactams such as **1** are amenable to α -alkylation of the Weinreb amide functionality, generating a quaternary center with predictable stereochemistry. The functional groups at C3 and C4 of the resultant β -lactams are transformed under standard conditions to provide building blocks for future synthetic ventures. In addition, the dianion of **24**, prepared from L-methionine in high yield, has been shown to undergo oxidative coupling to the corresponding diazabicyclo[3.2.0] heptane **16**. Further optimization of this transformation and elaboration of the product toward various products are ongoing and will be communicated in due course.

Experimental Section

General Procedures

Melting point determinations are uncorrected. Infrared spectra were recorded as thin films on salt plates, with ν_{\max} in inverse centimeters (cm^{-1}). High-resolution mass measurements were obtained on an ESITOF mass spectrometer. Flash chromatography was performed on Silica Gel 60, 40-63 mesh using EtOAc/hexanes mixtures as solvent unless otherwise indicated. Thin layer chromatography (TLC) was carried out on silica gel plates with UV detection. Proton (^1H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were obtained in CDCl_3 at 500 MHz, unless otherwise noted, and 125 MHz, respectively. The following abbreviations were utilized to describe peak patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, app = apparent, and m = multiplet. All air and moisture sensitive reactions were carried out under an atmosphere of dry nitrogen using oven-dried or flame-dried glassware and standard syringe techniques. Triethylamine (NEt_3), *N,N*-dimethylpropyleneurea (DMPU), benzylamine, and hexamethyldisilazane (HMDS) were distilled from calcium hydride. Allyl bromide was passed through a column of basic alumina immediately before use. *N,N*-Dimethylformamide was distilled sequentially from calcium hydride, then calcium oxide to remove trace amounts of dimethylamine. *N*-Bromosuccinimide was recrystallized from water. Tetrahydrofuran (THF), acetonitrile (CH_3CN), methylene chloride (CH_2Cl_2) and toluene were freshly obtained from the solvent purification system. Compounds **1**¹⁵ and **18**^{21,22} were prepared according to literature procedures. *N*-Methoxy-*N*-methylacetamide was prepared by a procedure described in the literature.²⁵ Single-crystal data were recorded using a Bruker SMART APEX II CCD area detector X-ray diffractometer using graphite monochromated Mo- $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The structures were solved by direct methods and expanded routinely. The models were refined by full-matrix least-squares analysis of F^2 against all reflections. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. Thermal parameters for the hydrogen atoms were tied to the isotropic thermal parameter of the atom to which they are bonded. Programs used: APEX-II v2.1.4²⁶; SHELXTL v6.14.^{27,28}

(2*R*,3*R*)-2-(Benzyloxymethyl)-3-ethyl-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetidone-3-carboxamide (**3**). To a suspension of potassium hydride (30-35% in mineral oil, 141 mg, 1.056 mmol, 1.1 equiv) in THF (10 mL) at -78°C was added the *trans*- β -lactam **1** (500 mg, 0.960 mmol, 1 equiv). The solution was stirred for 30 min, after which ethyl iodide (84 μL , 1.06 mmol, 1.1 equiv) was added. The resulting solution was stirred overnight while slowly warming to room temperature, after which TLC (30% EtOAc / Hexanes)

indicated consumption of starting material. The reaction was quenched with sat. NH_4Cl (10 mL) and the aqueous phase extracted with dichloromethane (3 x 10 mL). The combined organics were washed with brine (5 mL), dried (MgSO_4), and concentrated to obtain the title compound (268 mg) and its C3 epimer (116 mg) as colorless solids ($dr = 2.3:1$, 73% combined yield). Major isomer: mp = 118-122°C; $[\alpha]_D^{24} = 62.8$ ($c = 0.382$, CH_2Cl_2) ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.30-7.17 (m, 20H), 4.09 (d, $J = 11.0$ Hz, 1H), 3.90 (d, $J = 11.5$ Hz, 1H), 3.55 (s, 1H), 3.39 (s, 3H), 3.17 (m, 1H), 2.92 (s, 3H), 2.34-2.22 (m, 2H), 1.76 (m, 1H), 1.00 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 168.3, 142.9, 138.0, 130.2, 128.3, 127.9, 127.8, 127.6, 127.5, 73.7, 73.2, 66.1, 64.4, 62.1, 61.8, 33.1, 29.9, 9.5; IR (thin film) [cm^{-1}]: $\nu = 3056, 2879, 1748, 1639, 1452, 1275, 1104, 749, 699$; HRMS for $\text{C}_{35}\text{H}_{36}\text{N}_2\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$] calcd., 571.2567, found, 571.2539 (Error = -4.88 ppm).

(2R,3R)-3-Allyl-2-((benzyloxy)methyl)-N-methoxy-N-methyl-4-oxo-1-tritylazetidine-3-carboxamide (4). To a suspension of potassium hydride (110 mg, 0.960 mmol, 2 equiv) and sodium iodide (7 mg, 0.096 mmol, 0.1 equiv) in tetrahydrofuran (10 mL) at room temperature was added β -lactam **1**. The solution was stirred for 30 min, then cooled to -78 °C and allyl bromide (45 μL , 0.502 mmol, 1.1 equiv) was added. The solution was stirred overnight while slowly being allowed to warm to room temperature. TLC (50%EtOAc/Hex) indicated complete consumption of starting material. The reaction was quenched with sat. NH_4Cl (20 mL). The mixture was concentrated and extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (50 mL) and dried (MgSO_4). Concentration and purification by flash chromatography (50% EtOAc/Hex) afforded 215 mg of **4** as a colorless solid and 34 mg of its C3-epimer as a colorless solid (93% combined yield, $dr = 6:1$). mp = 118-120 °C; $[\alpha]_D^{24} = +16.9$ ($c = 4.5$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.37-7.25 (m, 20H), 5.97 (app. sex, $J = 8.0$ Hz, 1H), 5.13 (d, $J = 17.0$ Hz, 1H), 5.05 (d, $J = 10.0$ Hz, 1H), 4.17 (d, $J = 11.0$ Hz, 1H), 4.00 (d, $J = 11.0$ Hz, 1H), 3.69 (s, 1H), 3.45 (s, 3H), 3.24 (d, $J = 6.0$ Hz, 1H), 2.98 (m, 4H), 2.57 (d, $J = 6.0$ Hz, 1H), 2.36 (app. s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 167.6, 142.8, 138.0, 132.9, 130.2, 128.3, 128.0, 127.8, 127.7, 127.5, 118.9, 74.0, 73.2, 66.1, 63.6, 61.8, 61.3, 40.3, 33.1; IR (thin film) [cm^{-1}]: $\nu = 3062, 3032, 2931, 1751, 1640, 1599, 1493, 1449, 730, 700$; HRMS for $\text{C}_{36}\text{H}_{37}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}$] calcd., 561.2748, found, 561.2738 (Error = -1.75 ppm). X-ray quality crystals were obtained by slow evaporation of a CH_2Cl_2 /hexanes mixture.

(2R,3S)-3-Allyl-2-((benzyloxy)methyl)-N-methoxy-N-methyl-4-oxo-1-tritylazetidine-3-carboxamide. mp = 151-154 °C; $[\alpha]_D^{24} = +27.4$ ($c = 3.4$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.36-7.22 (m, 20H), 5.78 (ddt, $J = 17.0, 10.0, 7.0$ Hz, 1H), 5.06 (d, $J = 17.5$ Hz, 1H), 5.03 (d, $J = 10.0$ Hz, 1H), 4.54 (s, 1H), 4.10 (d, $J = 11.0$ Hz, 1H), 3.92 (d, $J = 11.0$ Hz, 1H), 3.70 (s, 3H), 3.31-3.28 (m, 4H), 3.10-3.09 (m, 2H), 2.34 (dd, $J = 4.5, 13.0$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 169.5, 166.2, 142.5, 137.5, 133.9, 130.0, 128.5, 128.2, 127.9, 127.8, 127.5, 117.9, 73.8, 73.3, 66.3, 64.8, 61.7, 61.2, 47.9, 32.3; IR (thin film) [cm^{-1}]: $\nu = 3064, 3032, 2932, 2862, 1755, 1642, 1493, 1444, 1345, 732, 700$; HRMS for $\text{C}_{36}\text{H}_{37}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}$] calcd., 561.2748, found, 561.2732 (Error = -2.73 ppm).

(3S,4R)-3-Acetyl-3-allyl-4-(benzyloxymethyl)-1-tritylazetididin-2-one (5). To a solution of allyl β -lactam **4** (612 mg, 1.09 mmol, 1 equiv) in THF (11 mL) at -41°C was added methyllithium (as a 1.6 M solution in ether, 1.87 mL, 2 equiv). The solution was stirred for 30 min, after which TLC (30% EtOAc/hexane) showed complete consumption of starting material. The solution was quenched with methanol, warmed to room temperature, and concentrated. The residue was partitioned between

dichloromethane (25 mL) and sat. NH_4Cl (25 mL) and the aqueous layer extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO_4) and concentrated to obtain the product (539 mg, 96% yield) as a colorless solid. mp = 96-99 °C; $[\alpha]_D^{26} = -35.7$ (c = 0.28, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.37-7.22 (m, 20H), 5.96 (dddd, $J = 6.7, 8.1, 10.1, 16.9$ Hz, 1H), 5.12 (d, $J = 17.0$ Hz, 1H), 5.07 (d, $J = 10.5$ Hz, 1H), 4.03 (d, $J = 10.0$ Hz, 1H), 3.86 (d, $J = 10.5$ Hz, 1H), 3.73 (s, 1H), 3.12 (d, $J = 10.5$ Hz, 1H), 2.71 (dd, $J = 8.5, 14.0$ Hz, 1H), 2.60 (dd, $J = 6.5, 13.5$ Hz, 1H), 2.19 (s, 3H), 1.97 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 205.2, 168.6, 142.7, 137.1, 132.3, 130.2, 129.0, 128.5, 128.2, 127.8, 127.7, 119.4, 74.1, 73.2, 65.2, 64.0, 39.2, 31.2; IR (thin film) [cm^{-1}]: $\nu = 3063, 3032, 2926, 2867, 1747, 1705, 1640, 1598, 1494, 1444, 1350, 699$; HRMS for $\text{C}_{35}\text{H}_{33}\text{NO}_3\text{Na}$ [M+Na] calcd., 538.2353, found, 538.2362 (Error = 1.66 ppm).

(2*R*,3*R*)-2-((Benzyloxy)methyl)-*N*-methoxy-*N*-methyl-4-oxo-3-(2-oxoethyl)-1-tritylazetidine-3-carboxamide (**6**). To a solution of allyl β -lactam **4** (149 mg, 0.27 mmol) in acetone/ H_2O (2.5 mL, 9:1) was added *N*-methylmorpholine-*N*-oxide (53 mg, 0.45 mmol, 1.7 equiv) and osmium tetroxide (as a solution in *t*-BuOH, 67 μL , 5.3 μmol , 0.02 equiv) and the resulting solution was allowed to stir overnight in the dark. TLC (50% EtOAc/hexane) showed complete consumption of starting material. Sodium periodate (114 mg, 0.53 mmol, 2 equiv) was added and the solution was stirred for an additional 2.5 h. The suspended solid was removed by vacuum filtration and the solution concentrated under vacuum. The residue was resuspended in water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with sat. sodium thiosulfate (30 mL), brine (30 mL), dried (MgSO_4), and concentrated to obtain **6** (120 mg, 81% yield) as a colorless solid. mp = 56 °C (decomposition); $[\alpha]_D^{25} = +38.1$ (c = 0.173, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ (ppm) 9.83 (dd, $J = 1.0, 2.5$ Hz, 1H), 7.37-7.26 (m, 20H), 4.18 (d, $J = 11.0$ Hz, 1H), 4.10 (d, $J = 11.0$ Hz, 1H), 3.99 (dd, $J = 2.0, 5.5$ Hz, 1H), 3.54 (s, 3H), 3.06 (s, 3H), 2.98 (d, $J = 9.5$ Hz, 1H), 2.92 (d, $J = 16.0$ Hz, 1H), 2.87-2.82 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 198.5, 168.2, 166.4, 142.4, 137.5, 129.8, 128.3, 127.9, 127.7, 127.6, 74.0, 73.3, 66.4, 63.0, 61.8, 58.9, 47.1, 32.9; IR (thin film) [cm^{-1}]: $\nu = 3060, 2925, 1754, 1723, 1638, 1493, 1449, 1339, 751, 735, 700$; HRMS for $\text{C}_{35}\text{H}_{34}\text{N}_2\text{O}_5\text{Na}$ [M+Na] calcd., 585.2366, found, 585.2377 (Error = 1.88 ppm).

(2*R*,3*R*)-2-((Benzyloxy)methyl)-3-(2-hydroxyethyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetidine-3-carboxamide (**7**). To a solution of aldehyde **6** (118 mg, 0.210 mmol, 1 equiv) in MeOH (2 mL) at 0 °C was added sodium borohydride (24 mg, 0.631 mmol, 3 equiv). The solution was stirred for 30 min and concentrated to dryness. The residue was redissolved in CH_2Cl_2 (10 mL), washed with sat NH_4Cl (3 x 10 mL), brine (10 mL), dried (MgSO_4), and concentrated to afford the product **7** as a colorless solid (82 mg, 69% yield). mp = 80-83 °C; $[\alpha]_D^{24} = +50.4$ (c = 0.222, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.37-7.26 (m, 20H), 4.13 (d, $J = 11.0$ Hz, 1H), 4.02 (br-s, 1H), 3.95 (d, $J = 11.0$ Hz, 1H), 3.75-3.71 (m, 3H), 3.39 (s, 3H), 3.32 (d, $J = 10.5$ Hz, 1H), 2.61(ddd, $J = 2.0, 4.5, 14.0$ Hz, 1H), 2.22 (d, $J = 10.0$ Hz, 1H), 2.12 (ddd, $J = 4.0, 9.0, 13.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 169.5, 169.4, 142.2, 137.7, 130.0, 128.3, 128.1, 127.9, 127.7, 74.0, 73.2, 65.5, 64.3, 61.7, 61.2, 60.1, 39.1, 33.1; IR (thin film) [cm^{-1}]: $\nu = 3436, 3059, 2925, 1749, 1641, 1493, 1445, 1357, 752, 700$; HRMS for $\text{C}_{35}\text{H}_{37}\text{N}_2\text{O}_5$ [M+H] calcd., 565.2697, found, 565.2707 (Error = 1.77 ppm).

(2*R*,3*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetidine-3-carboxamide (**9**). To a solution of β -lactam **8**¹⁵ (301 mg, 0.699 mmol, 1 equiv) in dimethylformamide (1

mL) was added *tert*-butyldimethylsilyl chloride (158 mg, 1.05 mmol, 1.5 equiv) and imidazole (143 mg, 2.10 mmol, 3 equiv). The solution was stirred overnight, after which TLC (50% EtOAc/Hex) indicated complete consumption of starting material. The solution was diluted with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (3 x 50 mL), brine (50 mL), dried (MgSO₄), and concentrated. The resulting residue was purified by flash chromatography (15% EtOAc/Hex to 30% EtOAc/Hex) to obtain 328 mg (86% yield) of product **9** as a colorless solid. mp = 82-84 °C; $[\alpha]_D^{23} = +10$ (c = 0.8, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.34-7.29 (m, 15H), 4.56 (s, 1H), 4.28 (s, 1H), 3.80 (s, 3H), 3.25 (s, 3H), 3.13 (d, *J* = 11.5 Hz, 1H), 2.45 (d, *J* = 11.5 Hz, 1H), 0.88 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 167.9, 163.7, 142.2, 130.1, 127.9, 127.6, 74.1, 62.5, 60.7, 57.6, 51.1, 32.4, 25.9, 25.8, 18.4, -5.3, -5.7; IR (thin film) [cm⁻¹]: ν = 3060, 3033, 2954, 2930, 2857, 1755, 1658, 1445, 1348, 735, 701; HRMS for C₃₂H₄₀N₂O₄SiNa [M+Na] calcd., 567.2655, found, 567.2681 (Error = 4.58 ppm).

(2*R*,3*S*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetidene-3-carboxamide (**10**). To a solution of β-lactam **8**¹⁵ (682 mg, 1.58 mmol, 1 equiv) in dimethylformamide (1.5 mL) was added *tert*-butyldiphenylsilyl chloride (1.24 μL, 4.75 mmol, 3 equiv), imidazole (324 mg, 4.75 mmol, 3 equiv), and triethylamine (662 μL, 4.75 mmol, 3 equiv). The solution was stirred for 10 h at 60 °C, after which TLC (50% EtOAc/Hex) indicated complete consumption of starting material. The solution was diluted with water (15 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were washed with water (3 x 30 mL), brine (5 mL), dried (MgSO₄), and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc/Hex to 30% EtOAc/Hex) to obtain 1.065 g (100% yield) of product **10** as a colorless solid. mp = 74-77 °C; $[\alpha]_D^{25} = +34.8$ (c = 3.0, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.54-7.24 (m, 25H), 4.73 (s, 1H), 4.32 (s, 1H), 3.78 (s, 3H), 3.25 (s, 3H), 3.07 (d, *J* = 12.0 Hz, 1H), 2.81 (dd, *J* = 4.0, 12.0 Hz, 1H), 1.07 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 167.7, 163.8, 142.3, 135.8, 135.7, 132.9, 132.7, 130.1, 129.9, 128.0, 127.8, 127.6, 74.2, 62.7, 61.8, 57.6, 51.4, 32.5, 27.1, 19.4; IR (thin film) [cm⁻¹]: ν = 3057, 2932, 2858, 1755, 1657, 1445, 1428, 1347, 739, 701; HRMS for C₄₂H₄₅N₂O₄Si [M+H] calcd., 669.3143, found, 669.3163 (Error = 3.01 ppm).

(2*R*,3*R*)-3-Allyl-2-(((*tert*-butyldimethylsilyloxy)methyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetidene-3-carboxamide (**11**). To a suspension of KH (147 mg, 1.10 mmol, 2 equiv) and NaI (8 mg, 0.055 mmol, 0.1 equiv) in THF (5 mL) at 0 °C was added *trans*-β-lactam **9** (300 mg, 0.551 mmol, 1 equiv). The solution was stirred for 1 h, after which allyl bromide (52 μL, 0.606 mmol, 1.1 equiv) was added. The reaction mixture was allowed to stir overnight while warming to room temperature. The solution was quenched with sat. NH₄Cl (10 mL) and the aqueous layer extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄), concentrated, and the residue purified by flash chromatography (gradient, 30% EtOAc/hexane to 70% EtOAc/hexane) to afford the title compound as a colorless solid (70 mg, 22% yield), along with the fused lactone / lactam **13** (22 mg, 10% yield) as a colorless solid. Analytical data for **11**: mp = 69-72 °C; $[\alpha]_D^{25} = +30.6$ (c = 5.8, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.29 (app. s, 15H), 6.03 (ddt, *J* = 10.0, 17.0, 7.0 Hz, 1H), 5.16 (dd, *J* = 2.0, 17.0 Hz, 1H), 5.05 (dd, *J* = 2.0, 10.0 Hz, 1H), 3.70 (dd, *J* = 3.0, 6.5 Hz, 1H), 3.50 (s, 3H), 3.20 (s, 4H), 3.07 (dd, *J* = 7.0, 14.0 Hz, 1H), 3.03 (app. s, 1H), 2.68 (dd, *J* = 7.0, 14.0 Hz, 1H), 0.79 (s, 9H), -0.16 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 167.6, 143.1, 133.6, 130.1, 127.9, 127.6, 118.4, 73.8, 65.5, 61.9, 60.9, 60.1, 40.5,

33.1, 26.0, 18.3, -5.2, -5.5; IR (thin film) [cm⁻¹]: ν = 3060, 2930, 1754, 1653, 1599, 1493, 1449, 776, 755, 734, 701; HRMS for C₃₅H₄₄N₂O₄SiNa [M+Na] calcd., 607.2968, found, 607.2990 (Error = 3.62 ppm).

(2*R*,3*R*)-3-Allyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetidene-3-carboxamide (**12**). To a suspension of potassium hydride (367 mg, 3.21 mmol, 3 equiv) and sodium iodide (16 mg, 0.11 mmol, 0.1 equiv) in THF at 0 °C was added the *trans*- β -lactam **10** (715 mg, 1.07 mmol, 1 equiv). The solution was stirred for 30 min, after which allyl bromide (185 μ L, 2.14 mmol, 2 equiv) was added. The resulting solution was warmed to room temperature and stirred overnight, after which TLC (30% EtOAc / Hexanes) indicated consumption of starting material. The reaction was quenched with sat. NH₄Cl (1 mL) and the aqueous phase extracted with EtOAc (3 x 1 mL). The combined organics were washed with brine (5 mL), dried (MgSO₄), and concentrated to obtain the title compound **12** (621 mg, 82% yield) as a single diastereomer. mp = 60-63 °C; $[\alpha]_D^{25}$ = +33.6 (c = 3.65, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.46-7.32 (m, 10H), 7.17-7.13 (m, 15H), 6.06 (app. ddt, *J* = 7.0, 10.0, 17.0 Hz, 1H), 5.23 (d, *J* = 17.0 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 3.76 (dd, *J* = 3.5, 10.0 Hz, 1H), 3.68 (app. t, *J* = 10 Hz, 1H), 3.41 (s, 3H), 3.20 (dd, *J* = 7.0, 14.0 Hz, 1H), 3.15 (s, 3H), 2.82 (dd, *J* = 3.5, 10.0 Hz, 1H), 2.66 (dd, *J* = 7.0, 14.0 Hz, 1H), 0.94 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 167.7, 167.0, 142.8, 135.9, 134.0, 133.6, 133.5, 129.7, 129.6, 127.8, 127.6, 127.4, 118.5, 73.7, 65.0, 62.3, 61.7, 60.8, 39.7, 32.9, 26.8, 19.2; IR (thin film) [cm⁻¹]: ν = 3071, 2933, 2858, 1754, 1653, 736, 701; HRMS for C₄₅H₄₈N₂O₄SiNa [M+Na] calcd., 731.3281, found, 731.3301 (Error = 2.73 ppm).

(1*R*,5*R*)-1-Allyl-6-trityl-3-oxa-6-azabicyclo[3.2.0]heptane-2,7-dione (**13**). To a solution of β -lactam **12** (101 mg, 0.14 mmol, 1 equiv) in THF (0.57 mL) was added TBAF (1 M solution in THF, 0.43 mL, 3 equiv). The resulting solution was refluxed for 16 h. The solution was quenched with sat. aq. NH₄Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, and concentrated. Flash chromatography (15% EtOAc/Hex to 50% EtOAc/Hex) afforded the title compound **13** (35 mg, 60% yield) as a colorless solid. mp = 158-160 °C; $[\alpha]_D^{24}$ = +105.5 (c = 1.83, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.35-7.34 (m, 9H), 7.14-7.12 (m, 6H), 5.82 (ddt, *J* = 10.0, 17.0, 7.5 Hz, 1H), 5.26 (dd, *J* = 1.0, 17.0 Hz, 1H), 5.20 (dd, *J* = 1.0, 10.0 Hz, 1H), 4.45 (d, *J* = 4.5 Hz, 1H), 3.74 (dd, *J* = 4.5, 11.5 Hz, 1H), 3.25 (d, *J* = 11.5 Hz, 1H), 2.80 (d, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 171.4, 162.6, 141.7, 131.5, 129.7, 128.5, 128.3, 120.4, 74.8, 68.6, 62.8, 58.4; IR (thin film) [cm⁻¹]: ν = 3060, 2928, 2856, 1787, 1751, 1598, 1492, 1445, 741, 700; HRMS for C₂₇H₂₄NO₃ [M+H] calcd., 410.1756, found, 410.1764 (Error = 1.95 ppm).

(3*S*,4*R*)-3-Acetyl-3-allyl-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-tritylazetidene-2-one (**14**). To a solution of allyl β -lactam **12** (50 mg, 70.5 μ mol, 1 equiv) in THF (1 mL) at -41 °C was added methyllithium (as a 1.6M solution in ether, 0.26 mL, 6 equiv). The solution was stirred for 30 min, after which TLC (30% EtOAc/hexane) showed complete consumption of starting material. The solution was quenched with methanol, warmed to room temperature, and concentrated. The residue was partitioned between CH₂Cl₂ (5 mL) and sat. aq. NH₄Cl (5 mL) and the aqueous layer extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄) and concentrated to obtain the product **14** (42 mg, 89% yield) as a colorless solid. mp = 63-67 °C; $[\alpha]_D^{26}$ = +11.8 (c = 3.35, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.47-7.45 (m, 5H), 7.41-7.34 (m, 5H), 7.21-7.12 (m, 15H), 5.90 (ddt, *J* = 10.0, 17.0, 7.0 Hz, 1H), 5.20 (dd, *J* = 1.0, 17.0 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 3.78 (dd, *J* = 7.8, 3.7 Hz,

1H), 3.41 (dd, $J = 10.8, 7.9$ Hz, 1H), 2.97 (dd, $J = 10.9, 3.7$ Hz, 1H), 2.83 (dd, $J = 7.1, 14.0$ Hz, 1H), 2.74 (dd, $J = 7.2, 14.0$ Hz, 1H), 2.36 (s, 3H), 0.99 (d, $J = 9.5$ Hz, 9H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 204.8, 168.2, 142.5, 135.8, 132.8, 129.89, 129.74, 127.89, 127.76, 127.5, 119.4, 74.6, 67.0, 63.5, 61.3, 37.6, 30.3, 27.1, 19.3; IR (thin film) [cm^{-1}]: $\nu = 3070, 2926, 2855, 1755, 1712, 1590, 1491, 1449, 822, 741, 701$; HRMS for $\text{C}_{44}\text{H}_{45}\text{NO}_3\text{SiNa}$ [$\text{M}+\text{Na}$] calcd., 686.3061, found, 686.3063 (Error = 0.27 ppm).

(1S,5R)-1-Allyl-2-hydroxy-2-methyl-6-trityl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one (15). To a solution of lactam **14** (401 mg, 0.60 mmol, 1 equiv) in THF (2.2 mL) was added TBAF (1M solution in THF, 1.8 mL, 3 equiv) and acetic acid (0.26 mL, 4.53 mmol, 7.5 equiv). The solution was stirred at reflux for 4 h, after which TLC (30% EtOAc/hexane) showed consumption of starting material. The solution was quenched with sat. aq. NaHCO_3 (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO_4 , and concentrated. The residue was purified by silica gel chromatography (25% EtOAc/Hex to 50% EtOAc/Hex) to afford the title compound **15** (177 mg, 69% yield) as a colorless solid. mp = 174-177 °C; $[\alpha]_D^{24} = +66.7$ ($c = 2.0, \text{CH}_2\text{Cl}_2$); ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.29 (app. s, 9H), 7.16 (app. s, 6H), 6.03 (app. dp, $J = 7.5, 9.7$ Hz, 1H), 5.25 (d, $J = 16.9$ Hz, 1H), 5.15 (d, $J = 9.7$ Hz, 1H), 4.11 (d, $J = 2.0$ Hz, 1H), 3.47 (dd, $J = 10.7, 2.0$ Hz, 1H), 2.75 (d, $J = 10.7$ Hz, 1H), 2.66-2.57 (m, 2H), 2.09 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 168.1, 142.7, 134.3, 130.1, 127.9, 127.7, 118.9, 102.5, 74.4, 67.8, 65.4, 63.2, 30.8, 23.5; IR (thin film) [cm^{-1}]: $\nu = 3411, 3060, 2984, 2935, 1730, 1642, 1598, 1493, 1445, 737, 701$; HRMS for $\text{C}_{28}\text{H}_{27}\text{NO}_3$ [$\text{M}+\text{H}$] calcd., 426.2064, found, 426.2072 (Error = 2.02 ppm).

2-((3S)-2-Hydroxy-3-(tritylamino)tetrahydrofuran-2-yl)-N-methoxy-N-methylacetamide (19). Hexamethyldisilazane (14.0 mL, 67.0 mmol, 2.3 equiv) was dissolved in dry THF (50 mL) and cooled to 0 °C. A solution of *n*-BuLi (2.5 M solution in hexanes, 25.6 mL, 64.1 mmol, 2.2 equiv) was added and the mixture was stirred for 15 min at 0 °C. The solution was cooled to -78 °C and *N*-methoxy-*N*-methylacetamide (6.5 mL, 61.2 mmol, 2.1 equiv) was added dropwise. The mixture was stirred for 45 min at -78 °C and *N,N*-dimethylpropyleneurea (DMPU, 50 mL) was added. After stirring for an additional 15 min, a solution of lactone **18** (10.0 g, 29.1 mmol, 1 equiv) in THF (50 mL) was added, resulting in a deeply red solution. The cooling bath was replaced by an ice bath and the solution was allowed to warm to 0 °C and stirred for 2 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl , extracted with EtOAc, washed with brine, dried (MgSO_4) and concentrated. The resulting residue was dissolved in a minimal amount of CH_2Cl_2 and applied to a silica plug. The plug was first washed with 10% EtOAc/Hex. The product was then eluted with EtOAc, and the EtOAc was concentrated to obtain the title compound **19** as a colorless solid and was employed in the next reaction without purification. mp = 60-64 °C; $[\alpha]_D^{25} = -12.5$ ($c = 53, \text{CH}_2\text{Cl}_2$); ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.57 (d, $J = 7.5$ Hz, 6H), 7.26 (app. t, $J = 7.5$ Hz, 6H), 7.18 (t, $J = 7.5$ Hz, 3H), 3.81 (app. dt, $J = 3.5, 9.0$ Hz, 1H), 3.66 (s, 3H), 3.48 (app. q, $J = 8.0$ Hz, 1H), 3.20 (s, 3H), 2.96 (dd, $J = 8.0, 8.5$ Hz, 1H), 2.70 (d, $J = 15.5$ Hz, 1H), 2.56 (d, $J = 15.5$ Hz, 1H), 2.39 (br-s, 1H), 1.35 (app. quin, $J = 9.0$ Hz, 1H), 1.22 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 173.2, 147.1, 129.0, 128.0, 126.5, 102.8, 70.5, 64.9, 61.6, 60.2, 36.7, 31.9, 31.2; IR (thin film) [cm^{-1}]: $\nu = 3347, 3057, 2939, 2891, 1632, 1596, 1489, 1448, 1389, 771, 736, 709$; HRMS for $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}$] calcd., 447.2278, found, 447.2263 (Error = -3.34 ppm).

(*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methyl-3-oxo-4-(tritylamino)hexanamide (**20**). To a solution of the above lactol **19** (2.384 g, 5.01 mmol, 1 equiv) in freshly distilled dimethylformamide (5 mL) was added *tert*-butyldimethylsilyl chloride (1.133 g, 7.52 mmol, 1.5 equiv) and imidazole (682 mg, 10.0 mmol, 3 equiv). The resulting solution was stirred overnight, after which TLC (30% EtOAc/Hex) indicated complete consumption of starting material. The solution was diluted in water (25 mL) and extracted with EtOAc (3 x 50 mL) and the combined organics washed with water (3 x 75 mL), brine (75 mL), dried (MgSO₄), and concentrated to afford 2.60 g of product **20** (92% yield) as a thick oil and was used without further purification. An analytically pure sample was obtained by flash chromatography (25% EtOAc/Hex to 50% EtOAc/Hex) as a mixture of keto and enol tautomers (approx.. 2.5:1 ratio; ¹H NMR data shown with major isomer H-count in whole integers and minor isomer H-count as decimals). [α]_D²⁶ = +7.3 (c = 3, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.52-7.49 (m, 2.4H), 7.47-7.44 (m, 6H), 7.28-7.13 (m, 12.6H), 5.05 (s, 0.4H), 3.80-3.61 (m, 3.8H), 3.60 (s, 1.2H), 3.54 (s, 3H), 3.46-3.41 (m, 2H), 3.34-3.28 (m, 0.4H), 3.27-3.23 (m, 1H), 3.13 (s, 1.2H), 3.12 (s, 3H), 3.07 (s, 0.4H), 3.04-3.01 (m, 0.4H), 1.90-1.82 (m, 1.4H), 1.67-1.60 (m, 1H), 1.53-1.46 (m, 0.4H), 0.85 (s, 9H), 0.82 (s, 3.6H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 2.4H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 207.4, 178.3, 171.7, 168.2, 146.9, 146.4, 129.2, 128.0, 127.8, 126.7, 126.4, 87.4, 71.5, 61.4, 61.3, 60.7, 60.0, 59.8, 55.1, 44.2, 37.1, 36.2, 32.0, 26.0, 25.9, 18.3, -5.4; IR (thin film) [cm⁻¹]: ν = 3435, 2954, 2856, 2102, 1633, 1471, 1447, 1254; HRMS for C₃₃H₄₄N₂O₄NaSi [M+Na] calcd., 583.2963, found, 583.2978 (Error = 2.6 ppm).

(*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-diazo-*N*-methoxy-*N*-methyl-3-oxo-4-(tritylamino)hexanamide (**21**). To a solution of β -ketoamide **20** (6.3 g, 11.2 mmol) in acetonitrile (140 mL) was added methanesulfonyl azide (1.5 mL, 16.9 mmol, 1.5 equiv) and 1,8-diazabicyclo[2.2.0]undec-1-ene (DBU, 2.2 mL, 14.6 mmol, 1.3 equiv). The mixture was stirred at room temperature under nitrogen for 4 h, concentrated and filtered over a plug of silica (elution with hexanes/EtOAc 3:1). The clear solution was again concentrated and the remaining solid was crystallized from CH₂Cl₂/hexanes to obtain 6.4 g (97% yield) of **21** as a colorless solid. mp = 124 °C (decomposition); [α]_D²⁵ = -28.0 (c = 3.8, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.50-7.52 (m, 6H), 7.20-7.23 (m, 6H), 7.13-7.16 (m, 3H), 4.64-4.71 (m, 1H), 3.85 (app. t, *J* = 7.4 Hz, 2H), 3.61 (s, 3H), 3.48 (d, *J* = 10.6 Hz, 1H), 3.12 (s, 3H), 1.98-2.05 (m, 1H), 1.83-1.90 (m, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 196.1, 162.3, 146.6, 129.2, 127.8, 126.4, 71.2, 61.2, 60.3, 56.7, 38.0, 33.7, 26.0, 18.4, -5.2; IR (thin film) [cm⁻¹]: ν = 3310, 3057, 2953, 2929, 2114, 1641, 1362, 1187, 1091; HRMS for C₃₃H₄₃N₄O₄Si [M+H] calcd., 587.3048, found, 587.3069 (Error = 3.6 ppm).

(2*S*,3*S*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetid-3-carboxamide (**22**). Method A: A degassed solution of α -diazo- β -ketoamide **21** (5.7 g, 9.7 mmol, 1 equiv) in dry toluene (1 L), was cooled to 0 °C and irradiated with a medium pressure mercury vapor lamp for 4.5 h. DBU (7.2 mL, 48.5 mmol, 5 equiv) was added and the mixture was stirred at room temperature overnight, concentrated and filtered over a plug of silica (elution with EtOAc/hexanes 1:1). After removal of the solvents the remaining oil was redissolved in EtOAc, washed with saturated aqueous NH₄Cl, water and brine and dried over MgSO₄. Concentration afforded **22** as a white foam (5.0 g, 92% yield) which was used for the next step without further purification. Analytical data were obtained from

the crystalline solid after purification by flash chromatography on silica gel (elution with hexanes/EtOAc 2:1, 1:1).

Method B: To a degassed solution of α -diazo- β -ketoamide **21** (2.46 g, 4.19 mmol, 1 equiv) in dry toluene (1 L) was added DBU (3.1 mL, 21.0 mmol, 5 equiv). The resulting solution was refluxed under N₂ for 1 h. After cooling to room temperature, the solution was washed with aq. 5% citric acid (3 x 100 mL), brine (50 mL), dried over MgSO₄, and concentrated to afford the title compound (2.09 g, 89% yield) as a colorless solid which was used for the next step without further purification. mp = 92-94 °C; $[\alpha]_D^{26} = +2.0$ (c = 2.6, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.26-7.34 (m, 15H), 4.39 (br d, *J* = 10.6 Hz, 1H), 4.35 (br s, 1H), 3.82 (s, 3H), 3.42-3.46 (m, 1H), 3.33-3.38 (m, 1H), 3.26 (s, 3H), 1.43-1.50 (m, 1H), 0.97-1.02 (m, 1H), 0.82 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 167.6, 163.9, 142.4, 129.9, 128.0, 127.6, 74.0, 62.6, 60.3, 56.3, 35.6, 32.3, 25.9, 18.3, -5.6, -5.7; IR (thin film) [cm⁻¹]: ν = 3059, 2953, 2928, 2856, 1752, 1657, 1445, 1101; HRMS for C₃₃H₄₃N₂O₄Si [M+H] calcd., 559.2987, found, 559.2982 (Error = -0.8 ppm).

(2*S*,3*S*)-2-(2-Hydroxyethyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetid-3-carboxamide (**17**). TBAF (1 M in THF, 10.8 mL, 1.5 equiv) was added to a solution of lactam **22** (4.0 g, 7.2 mmol, 1 equiv) in THF (4 mL) at room temperature. The mixture was stirred for 2 h and concentrated under a stream of nitrogen. The residue was dissolved in EtOAc, washed with saturated aqueous NH₄Cl, water and brine, dried (Na₂SO₄) and concentrated. Purification by flash chromatography on silica gel (elution with EtOAc/hexanes 6:1 to 8:1) yielded the product **17** as a white foam (2.9 g, 91%). mp = 113-115 °C; $[\alpha]_D^{25} = +13.6$ (c = 3.3, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.27-7.34 (m, 15H), 4.40 (br d, *J* = 10.5 Hz, 1H), 4.28 (br s, 1H), 3.81 (s, 3H), 3.39-3.50 (m, 2H), 3.27 (s, 3H), 1.47-1.54 (m, 1H), 1.36 (br s, 1H), 0.96-1.03 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 167.6, 163.5, 142.3, 128.9, 128.1, 127.6, 74.1, 62.6, 59.7, 56.5, 55.9, 35.4, 32.4; IR (thin film) [cm⁻¹]: ν = 3466, 3058, 2941, 1747, 1651, 1492, 1445; HRMS for C₂₇H₂₉N₂O₄ [M+H] calcd., 445.2122, found, 445.2116 (Error = -1.4 ppm).

2-((2*S*,3*S*)-3-(Methoxy(methyl)carbamoyl)-4-oxo-1-tritylazetid-2-yl)acetic acid (**23**). To a biphasic solution of alcohol **17** (748 mg, 1.683 mmol, 1 equiv) in CCl₄ / CH₃CN / H₂O (11.2 mL, 2:2:3) was added NaIO₄ (1.080 g, 5.049 mmol, 3 equiv) and RuCl₃·xH₂O (10 mg, 0.034 mmol, 0.02 equiv) and the resulting solution was stirred vigorously overnight at room temp. The resulting brownish suspension was quenched with brine / sat. Na₂S₂O₃ (1:1, 50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organics were dried (MgSO₄) and concentrated to obtain 680 mg (90%) of a slightly brownish solid which was recrystallized from EtOAc. mp = 82 °C (decomposition); $[\alpha]_D^{25} = +27.5$ (c = 0.79, CH₂Cl₂); ¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 12.24 (br-s, 1H), 7.39-7.34 (m, 9H), 7.19 (d, *J* = 7.0 Hz, 6H), 4.41 (s, 1H), 4.22 (app. dt, *J* = 3.0, 11.0 Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.46 (dd, *J* = 10.5, 16.5 Hz, 1H), 1.31 (dd, *J* = 3.5, 17.0 Hz, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ (ppm) 171.3, 166.8, 163.1, 141.7, 129.4, 127.9, 127.6, 73.3, 61.7, 54.9, 53.0, 36.0, 31.8; IR (thin film) [cm⁻¹]: ν = 3143, 3059, 2973, 2940, 1750, 1737, 1655, 1492, 1446, 736, 701; HRMS for C₂₇H₂₇N₂O₅ [M+H] calcd., 459.1914, found, 459.1944 (Error = 6.4 ppm).

(2*S*,3*S*)-2-(2-(Benzylamino)-2-oxoethyl)-*N*-methoxy-*N*-methyl-4-oxo-1-tritylazetid-3-carboxamide (**24**). To a solution of acid **23** (250 mg, 0.545 mmol, 1 equiv) in CH₂Cl₂ (5.5 mL, 0.1 M) was added 1,1'-carbonyldiimidazole (97 mg, 0.60 mmol, 1.1 equiv). The resulting solution was stirred for 15 min, after

which benzylamine (117 mg, 1.090 mmol, 2 equiv) was added and the solution was allowed to stir at room temperature overnight. The reaction mixture was diluted to 10 mL with CH₂Cl₂, washed with sat. NH₄Cl (3 x 10 mL), brine (10 mL) and dried (MgSO₄). Concentration afforded the desired compound **24** (294 mg, 98 % yield) as a colorless solid which was recrystallized from EtOAc. mp = 91 °C (decomposition); $[\alpha]_D^{25} = +16.6$ (c = 1.2, CH₂Cl₂); ¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 8.19 (app. t, *J* = 5.5 Hz, 1H), 7.39-7.13 (m, 20H), 4.34-4.33 (m, 2H), 4.17 (dd, *J* = 6.0, 15.0 Hz, 1H), 4.09 (dd, *J* = 6.0, 15.5 Hz, 1H), 3.62 (s, 3H), 3.18 (s, 3H), 2.35 (dd, *J* = 11.5, 15.0 Hz, 1H), 1.45 (dd, *J* = 3.0, 14.0 Hz, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ (ppm) 168.4, 166.5, 162.8, 141.6, 139.0, 129.2, 128.1, 127.8, 127.4, 127.0, 126.6, 73.2, 61.6, 54.5, 53.9, 41.8, 37.8, 31.7; IR (thin film) [cm⁻¹]: ν = 3424, 3061, 2929, 1754, 1657, 1652, 1543, 1494, 1446, 735, 700; HRMS for C₃₄H₃₃N₃O₄Na [M+H] calcd., 548.2544, found, 548.2555 (Error = 1.08 ppm).

(1R,5S)-2-Benzyl-N-methoxy-N-methyl-3,7-dioxo-6-trityl-2,6-diazabicyclo[3.2.0]heptane-1-carboxamide (16) **General Procedure:** A solution of the above secondary amide (55 mg, 0.10 mmol) in THF (1 mL) was cooled to -78 °C. A freshly prepared solution of LHMDS (0.17 mL, 1 M Solution in THF, 2.2 equiv) was added and the solution was stirred at -78 °C for 1 h. An oxidant (0.2 mmol, 2 equiv) was then added. The solution was warmed to 0 °C and allowed to stir for an additional 2 h before being quenched with aq. sat. NaHCO₃ (2 mL) and aq. sat. Na₂S₂O₃ (2 mL). After stirring for 5 min, the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with aq. sat. NH₄Cl (3 x 10 mL), Brine (10 mL), and dried over MgSO₄. The crude residue was then purified by flash chromatography (30% EtOAc / Hex to 100% EtOAc) to afford the desired product **16** as a colorless solid. mp = 80 °C (decomposition); $[\alpha]_D^{25} = +60.0$ (c = 0.72, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.46-7.02 (m, 20H), 4.71 (d, *J* = 14.5 Hz, 1H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.44 (d, *J* = 6.5 Hz, 1H) 3.40 (s, 3H), 3.02 (s, 3H), 2.16 (dd, *J* = 6.5, 18.5 Hz, 1H), 1.72 (d, *J* = 18.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 173.8, 163.2, 142.0, 136.1, 129.9, 129.8, 128.8, 128.3, 128.1, 127.8, 74.4, 61.3, 56.1, 46.8, 44.8, 34.7, 32.7; IR (thin film) [cm⁻¹]: ν = 3061, 3027, 2934, 1765, 1702, 1662, 1494, 1445, 755, 733, 700; HRMS for C₃₄H₃₂N₃O₄ [M+H] calcd., 546.2387, found, 546.2408 (Error = 3.89 ppm).

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Supplementary data

Copies of ¹H NMR and ¹³C NMR spectra for all new compounds, along with an ORTEP depiction of **4**, are provided. Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2014.05.054>.

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