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Article

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Studies of Azetidin-2-one as a Reactive Enolate Synthon of β-Alanine for Condensations with Aldehydes and Ketones

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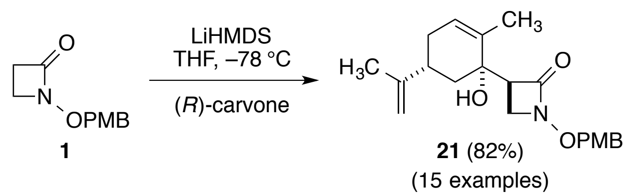
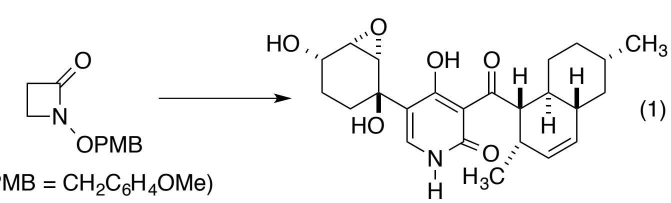


ABSTRACT: Studies describe formation of the lithium enolate of *N*-(4-methoxybenzyloxy)azetidin-2-one (**1**), and characterization of representative aldol reactions with aldehydes and ketones. Diastereoselectivity features the production of *anti*-aldol adducts from α,β-unsaturated ketones and α-branched aliphatic aldehydes. The stereoselectivity is rationalized via closed, six-membered transition state arrangements leading to the formation of Felkin-Anh and *anti*-Felkin products. Examples illustrate the direct incorporation of monocyclic β-lactams into a variety of molecular architectures. The utility of **1** as an enolate synthon of homoglycine (β-alanine) is illustrated by the efficient synthesis of novel β-amino acid derivatives, including complex 4-hydroxy-2-pyridinones.

INTRODUCTION

Small ring heterocycles have been widely utilized as reactive intermediates for the synthesis of complex heterocyclic systems. Azetidin-2-ones (β-lactams) are especially significant as an essential motif in penicillin and cephalosporin antibiotics. Recent methodology toward the synthesis of β-lactams has impressively advanced the Staudinger reaction of ketenes with various *N*-substituted imines for the preparation of 3,4-disubstituted and 4-monosubstituted examples.[1,2] In this manner, catalytic processes have been devised for the production of β-lactams with *cis*- and *trans*-diastereoselectivity, as well as high enantioselectivity.[3] However, these advances have not proven useful for the synthesis of 3-monosubstituted-2-azetidinones. Methods that feature the preparation of related azetidines as reactive species have also recently received attention,[4] and studies for the selective ring opening of the β-lactam have been reported.[5] The reactivity of azetidin-2-one provides for the design of peptidomimetics via the incorporation of a homoglycine (β-alanine) subunit within the amido backbone. For these examples, the introduction of substitution at the α-carbon (3-position) of the β-lactam ring can prove useful for the design of unnatural β-aminoamides as isosteric bioactive equivalents. In the course of our investigations leading to the total synthesis of apiosporamide,[6] we have explored the aldol reactions of *N*-(4-methoxybenzyloxy)azetidin-2-one (**1**) as an effective general strategy for the synthesis of complex, nonracemic 4-hydroxy-2-pyridinones, as exemplified by **2** and related natural products (Eq. 1).[7] Herein, we describe a full account of our investigations of aldol reactions of **1** and describe the contributing factors leading to the observed stereoselectivity of these processes.



1 (PMB = $CH_2C_6H_4OMe$)

2 ((+)-Apiosporamide)

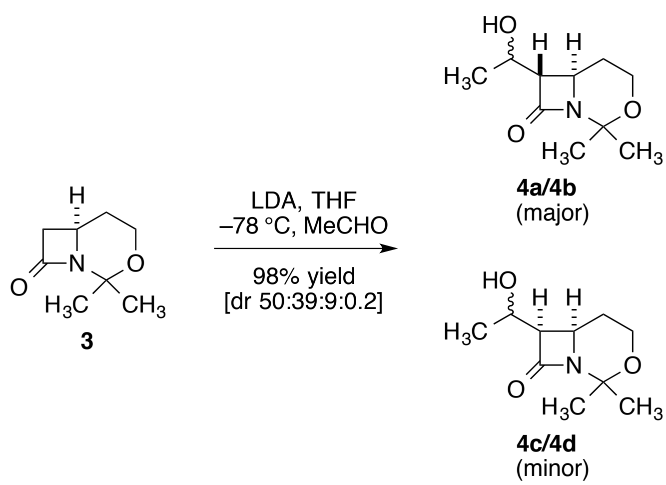
(1)

These studies have demonstrated a kinetic enolization of **1** and the reactivity of the resulting lithium enolate with a selection of aldehydes and ketones. Our efforts present a method for the direct incorporation of the intact β-lactam into complex molecular architectures which may serve as probes of biological targets.

RESULTS AND DISCUSSION

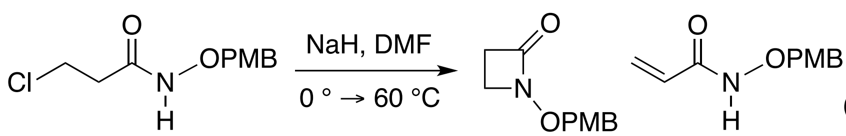
Studies of aldol reactions involving azetidin-2-one substrates have been associated, in large measure, with installation of the hydroxylethyl side chain of thienamycin and related penem derivatives.[8,9] The condensation of the enolate of **3** with acetaldehyde yields the adducts **4a-d** (Scheme 1). Chirality at C-4 of the starting azetidinone **3** determines the C-3 stereochemistry (**4ab**:**4cd** ratio 89:9), whereas only modest asymmetric induction is observed for introduction of chirality at the site of the secondary alcohol (**4a**:**4b** ratio 50:39). In related reports of acyclic systems, a stereoselective C-alkylation of the lithium enolate, derived from the deprotonation of methyl-3-aminobutyrate, has been shown to produce *anti*-stereoselectivity.[10]

Scheme 1. Aldol Reaction of 3 with Acetaldehyde



Our initial attempts to explore kinetic enolate formation of the parent azetidin-2-one examined several standard choices for nitrogen protection, and these derivatives failed to provide solutions of enolates consistent with stable, albeit reactive, species.

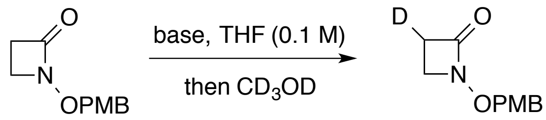
Based on literature reports by Miller and coworkers[11] regarding the preparation and bioactivity of *N*-alkoxyazetidin-2-ones, we have found that the presence of the N-O bond in the hydroxamic acid PMB (*para*-methoxybenzyl) derivative **1** leads to useful solutions of highly reactive enolates at –78 °C. The azetidin-2-one **1** is obtained by adapting the report of Reinhoudt[12] for intramolecular *N*-alkylation of 4-(4-methoxybenzyloxy)-3-chloropropionamide **5** using sodium hydride in DMF at 60 °C (Eq. 2). Small amounts of the acrylamide **6** are occasionally observed in the reaction, but the desired β-lactam **1** is



5 **1** (52%) **6** (2)

readily purified by flash chromatography and stored under anhydrous conditions as a crystalline solid (mp 46–47 °C). Studies for the kinetic deprotonation of **1** have measured deuterium incorporation to quantify enolate formation by the integration of the α-hydrogen signal in ^{1}H NMR spectra following the d_4-methanol quench. As summarized in Table 1, the choice of the base is significant for achieving complete deprotonation as LDA has proven to be less effective than LiHMDS (entries 1 and 2) whereas LiHMDS is superior to the use of the corresponding NaHMDS and KHMDS bases.[13] Notably, solutions of enolate show evidence of decomposition as temperatures are increased from –78 °C to –40 °C or above (entries 6 and 8).

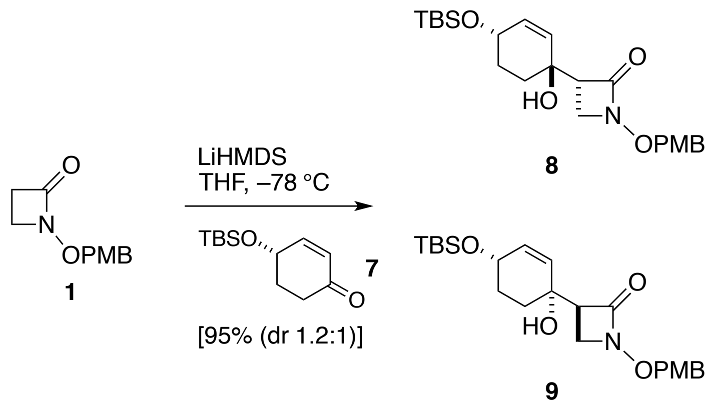
Table 1. Deprotonation Studies of 1



1 **1a**

entry	base	equiv	time	temp	% *d*-incorporation
1	LDA	1.1	1 h	–78 °C	69% D
2	LiHMDS	1.1	1 h	–78 °C	90% D
3	NaHMDS	1.1	1 h	–78 °C	79% D
4	KHMDS	1.1	1 h	–78 °C	12% D
5	NaHMDS	1.5	1 h	–78 °C	83% D
6	NaHMDS	1.1	1.3 h	–78 °C to 0 °C	decomp
7	LiHMDS	1.1	2 h	–78 °C	100% D
8	LiHMDS	0.93	2.2 h	–78 °C to –40 °C	decomp

By employing our optimized conditions, the enolate of **1** affords a facile condensation with the nonracemic enone **7** to produce nearly equal amounts of the *anti*-diastereomers **8** and **9** in 95% yield (Eq. 3). No products resulting from 1,4-conjugate addition are observed. Fortunately, the chromatographic separation of these diastereomers provides suitable crystals leading to simple derivatives of each alcohol for unambiguous assignments of stereochemistry via X-ray crystallographic analysis.[14]



(3)

Our mechanistic rationale of this aldol reaction considers four closed transition states as illustrated in Figure 1. The *anti*-products **8** and **9** arise via the Zimmerman–Traxler arrangements of **10** and **11**, respectively, whereas **12** and **13** lead to the unobserved *syn*-adducts **14** and **15**. Unfavorable steric interactions of the C-4 methylene of the enolate of **1** with the saturated methylene carbons of the starting cyclohexenone are destabilizing in **12** and **13**. This condition is remedied by the presence of the planar C=C moiety in both **10** and **11**, and a slight preference for formation of **8** is attributed to axial addition to the cyclohexenone carbonyl versus equatorial addition as featured in **11**.

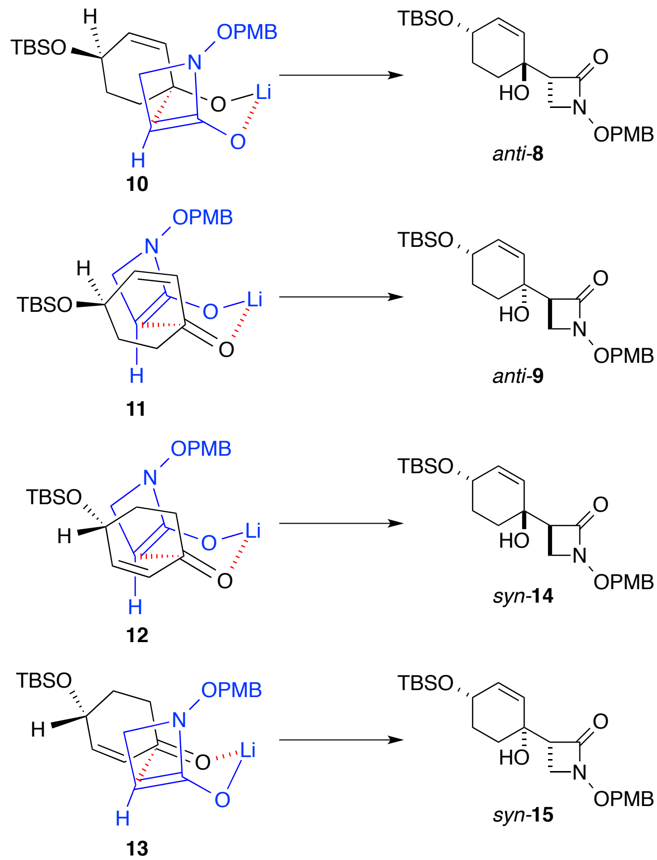
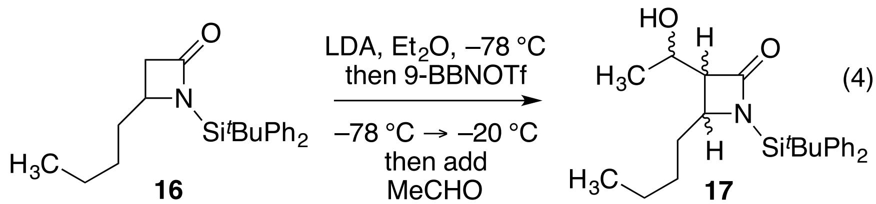


Figure 1. Zimmerman–Traxler arrangements leading to *anti*- and *syn*-aldol products of **1**.

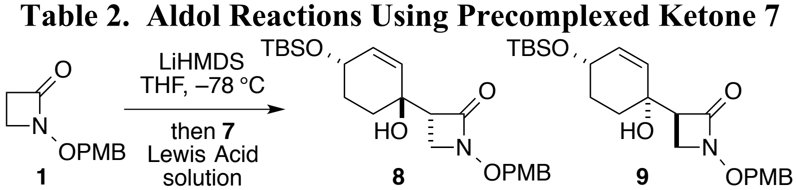
The total synthesis of (+)-apiosporamide has utilized *anti*-**8**,[6] and further studies have sought reaction conditions to maximize the production of the desired diastereomer. The addition of an equivalent of HMPA or 12-crown-4 into solutions of the lithium enolate, followed by reactions with enone **7**, result in a slight increase in the formation of **8** (dr 1.4:1). However, attempts to generate a boron enolate by the direct treatment of **1** with *n*-Bu_2BOTf and Et_3N or by the transmetalation of the lithium enolate upon the addition of *n*-Bu_2BOTf or 9-BBNOTf have led to the recovery of starting materials. The literature describes an example of an aldol competent boron enolate derived from the C-4 substituted-*N*-silyl β-lactam **16** (Eq 4).[15] Deprotonation with LDA at low temperature is followed by addition of 9-BBNOTf with warming to –20 °C. Subsequent introduction of acetaldehyde yields **17** (80%). Unfortunately, in our studies, the recovery of starting **1** is observed by application of these conditions.[16]



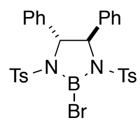
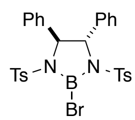
(4)

We have also investigated the use of Lewis acids for precomplexation of enone **7** as a means to modulate the outcome of our key aldol reaction. In fact, chiral Lewis acids would incorporate an additional element of stereocontrol for access to the desired facial selectivity. For these experiments, a concentrated solution of enone **7** and Lewis acid is premixed at –78 °C, and this solution is then transferred via cannula into a cold solution of the lithium enolate of **1**. Unoptimized results are summarized in Table 2 and feature a facile aldol condensation with minimal changes in stereoselectivity. Furthermore, the use of chiral Lewis acids (entries 5, 6, 7 and 8) indicate a slight increase in the preference for the *anti*-diastereomer **8** irrespective of the chirality of the Lewis acid. This behavior suggests small improvements in the reaction profile for axial versus equatorial addition, while elements of asymmetry in the Lewis acid do not affect the facial selectivity.

Table 2. Aldol Reactions Using Precomplexed Ketone 7

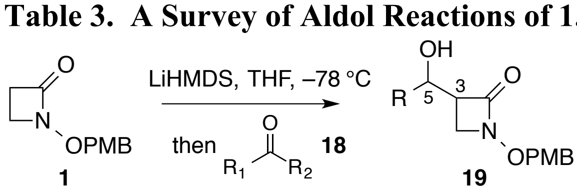


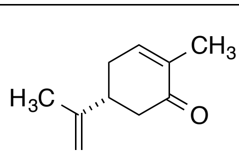
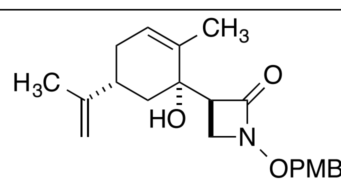
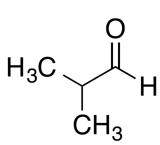
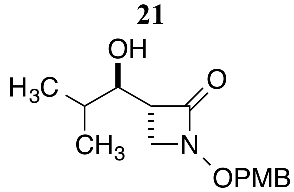
entry	Lewis acid	**8**:**9** ratio
1	$EtAlCl_2$	57:43
2	BF_3•OEt_2	55:45
3	$MgBr_2$•OEt_2	57:43

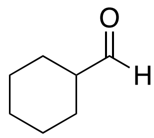
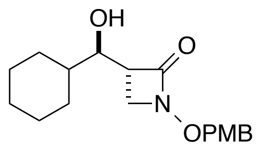
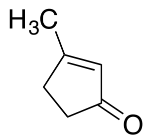
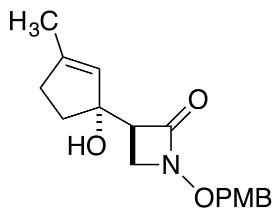
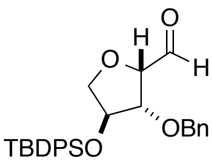
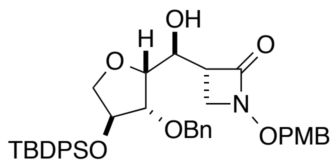
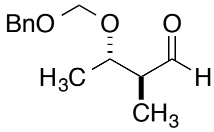
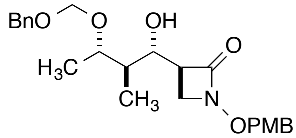
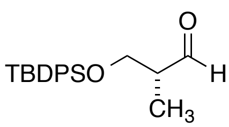
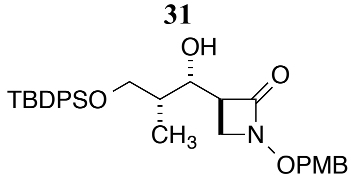
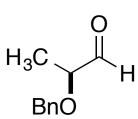
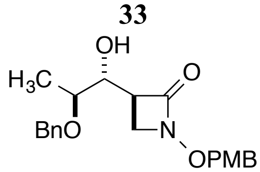
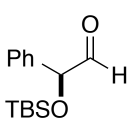
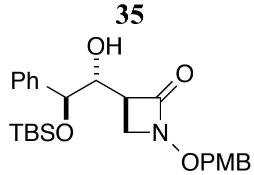
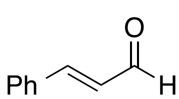
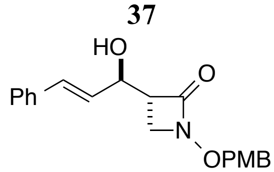
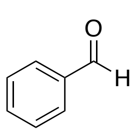
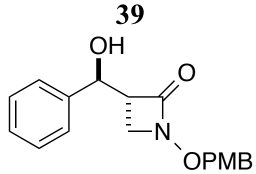
4	Ti(O-*i*-Pr)$_4$	59:41
5	Ti(O-*i*-Pr)$_4$/(*S*)-BINOL (2 equiv)	75:25
6	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL (2 equiv)	67:33
7		66:34
8		68:32

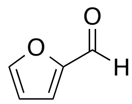
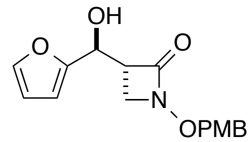
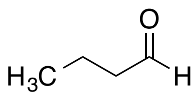
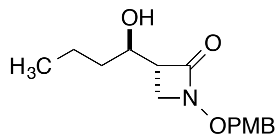
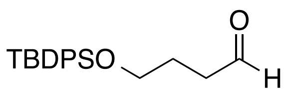
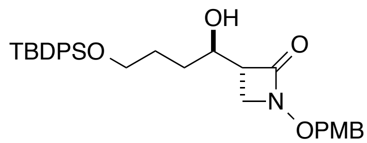
We have subsequently surveyed the scope of the aldol reaction using the lithium enolate of *N*-(4-methoxybenzyloxy)-azetidin-2-one (**1**) in reactions with a variety of aldehydes and ketones. A compilation of examples is shown in Table 3 based upon the application of the previous reaction conditions affording **8** and **9**.

Table 3. A Survey of Aldol Reactions of 1.



entry	substrate	major product[a]	yield (%)[b]	dr ratio[c] (*anti*:*syn*)	ratio of *anti*-isomers[d]
1	 **20**	 **21**	82	100:0	>96:4
2	 **22**	 **23**	97	94:6	n.a.

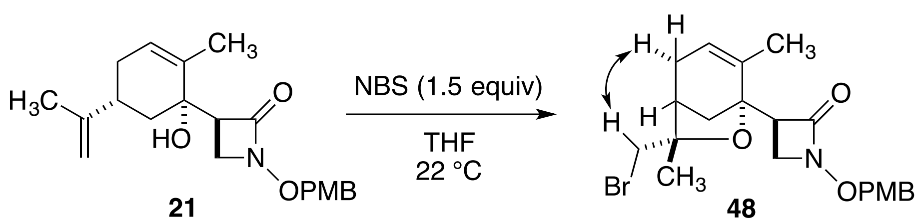
3	 **24**	 **25**	86	95:5	n.a.
4	 **26**	 **27**	72	75:25	n.a.
5	 **28**	 **29**	85	81:19	94:6
6	 **30**	 **31**	94	>96:4	75:25
7	 **32**	 **33**	80	>96:4	58:42
8	 **34**	 **35**	81	80:20	65:35
9	 **36**	 **37**	80	>96:4	53:47
10	 **38**	 **39**	90	70:30	n.a.
11	 **40**	 **41**	93	80:20	n.a.

12	 **42**	 **43**	93	83:17	n.a.
13	 **44**	 **45**	80	88:12	n.a.
14	 **46**	 **47**	87	89:11	n.a.

[a]In each example, the major product was isolated and characterized as a pure sample. [b]Yields are based upon an initial flash chromatography to provide the crude aldol adducts as a mixture of isomers which were separated from remaining starting substrates. [c]The ratios of diastereomers were determined by an integration of selected hydrogen signals. [d]*Anti*-isomers are characterized by larger J_{H3}–J_{H5} coupling constants in the 6–9 Hz range as compared to *syn*-isomers J_{H3}–J_{H5} = 1–4 Hz). Using simple aldehydes and ketones, a racemic product is obtained and n.a. is symbolized to indicate not applicable dr data in these cases.

Upon complete deprotonation of **1** using LiHMDS at –78 °C in THF, the reactive enolate provides for a rapid condensation upon introduction of the carbonyl substrate. Nucleophilic additions generally proceed in good to excellent yields. In these products, a significant pathway for decomposition is available through nucleophilic opening of the β-lactam ring. Thus, it is important to quench these aldol reactions with a pH 7 buffer, and to avoid prolonged reaction times since initially formed alkoxides, particularly those derived from starting aldehydes, can lead to O-acylation via intermolecular reactions at –78 °C. To achieve successful aldol reactions, anhydrous conditions are required and the starting β-lactam **1** should be free of impurities. We have noted that samples of **1**, which are stored for 7 days, often contain small amounts of impurities. The use of these samples without repurification lead to poor outcomes or failed reaction attempts. Our conditions have used a slight excess of the enolate of **1**, and the carbonyl substrate is generally consumed within 30 minutes at –78 °C. No evidence is observed for competing processes of deprotonation that lead to the reisolation of starting material, as might be anticipated in the case of 3-methylcyclopentenone **26**. Likewise, epimerization is not observed in the reactions of aldehydes **28**, **30**, **32**, **34**, and **36**. The aldol reaction of the enolate of **1** with aldehydes leads to the *anti*-products with good to excellent stereoselectivity for substrates that display increasing steric hindrance as a result of α-substitution (entries 2–9). In some cases, the corresponding *syn*-adducts are found as minor products. The assignment of relative stereochemistry is determined by an analysis of vicinal ^{1}H coupling constants. Isomers with the *anti*-stereochemistry show large (J_{H3}–J_{H5}) coupling in the range of 6–9 Hz compared to small coupling constants (J_{H3}–J_{H5} of 1–4 Hz) for the corresponding *syn*-diastereomers.[17] Thus, ratios of *anti*- to *syn*-diastereomers, derived from aldehyde substrates, can often be determined by an integration of selected ^{1}H NMR signals of samples of aldol product mixtures. In all cases, major products are fully characterized following an initial chromatography leading to isolation of the mixture of aldol adducts and repurification via flash (silica gel) chromatography. Attempts for preparative HPLC separations of diastereomers have displayed evidence of decomposition, which is not encountered in the flash chromatography efforts. Our studies of chiral, nonracemic aldehydes provide β-lactams with modest levels of asymmetric induction as a result of substrate control (Table 3; entries 5–9). For the products of representative examples (entries 7 and 8), the chirality of the secondary alcohol is confirmed via the Mosher ester analysis,[18] and closely related products (entries 6 and 9) were recognized by the similarities of features and coupling constants in the analysis of their proton NMR spectra. In the case of tertiary alcohol **21** (entry 1), additional information is obtained upon treatment with *N*-bromosuccinimide

(NBS) in THF at 22 °C (Eq 5). Cyclization proceeds to afford the bromide **48** as a single diastereomer in 73% yield, establishing the *cis*-stereochemistry of the starting alcohol and the isopropenyl substituent in **21**. NOESY studies have led to the assignment of the newly established stereogenic carbon by the observed crosspeak for the indicated hydrogens shown in **48**. The *anti*-stereochemistry of the major product **27** from ketone **26** (entry 4) is assumed by analogy to similarities with related products **8**, **9**, and **21**.



(5)

We have considered these results through the evolution of Felkin-Anh and *anti*-Felkin arrangements which lead to diastereomeric transition states. Thus, the major adduct **33** (dr 58:42) in entry 7 (Table 3) is rationalized by the Felkin–Anh model **49** (Figure 2), whereas its accompanying minor diastereomer **33a** is produced from the *anti*-Felkin arrangement **50**, which is modified by a C–C bond rotation to avoid the *syn*-pentane interaction with the C-4 methylene of the enolate. For the minimal energetic costs imposed by the C–C rotation in **50**, the *anti*-Felkin product is achieved with comparable steric effects as found in **49**. Similarly, the presence of α-benzyloxy substitution in nonracemic aldehyde **34** provides major adducts as predicted via the polar Felkin model **51** as well as the competing *anti*-Felkin **52** with a minimization of steric interactions (Figure 2). The competing aldol reactions, described by **51** and **52**, lead to the production of the major product **35** as well as the alternative *anti*-isomer **35a** (dr 65:35 for the *anti*-isomers).

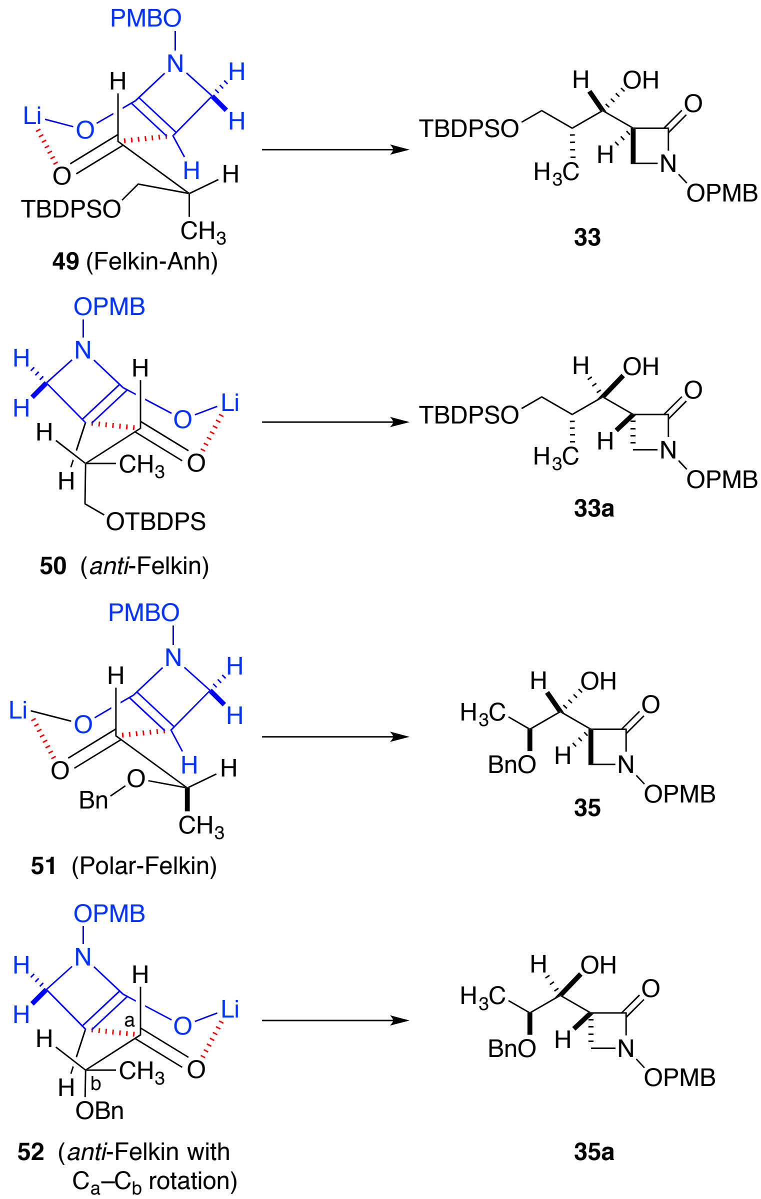
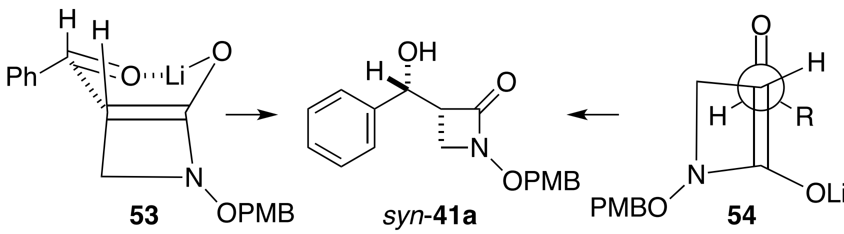


Figure 2. Considerations of asymmetric induction for reactions of α-substituted aldehydes with **1**.

The extent to which *syn*-aldol adducts are formed in certain cases was not anticipated. Our studies have found that aromatic and heteroaromatic aldehydes and straight chain aliphatic aldehydes usually indicate the production of *syn*-diastereomers, comprising as much as 12%–25% of the observed product mixture (Table 3; entries 10–14). We speculate that *syn*-products may arise from a closed boat-like transition state

(TS) **53** or from a competing periplanar open transition state **54** as illustrated for the formation of *syn*-**41a** (Scheme 2). The open TS arrangement **54** orients the aldehydic

Scheme 2. Open Transition State Arrangements

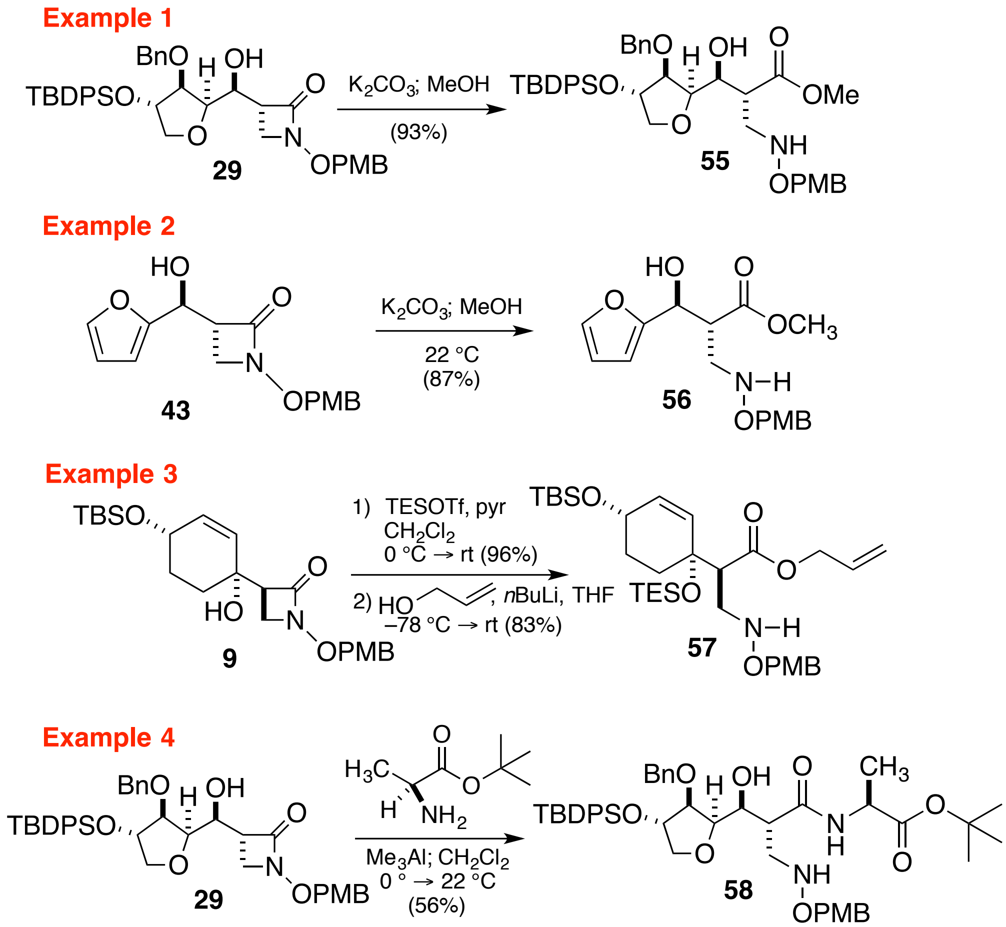


hydrogen over the β-lactam ring to minimize steric interactions. This may explain the absence of *syn*-adducts in the aldol reactions of **1** with many ketones. In addition, the presence of α-branching in aldehyde substrates increases the effective steric bulk of R, which may destabilize **54** relative to the closed TS arrangements due to nonbonded interactions with the lithium enolate.

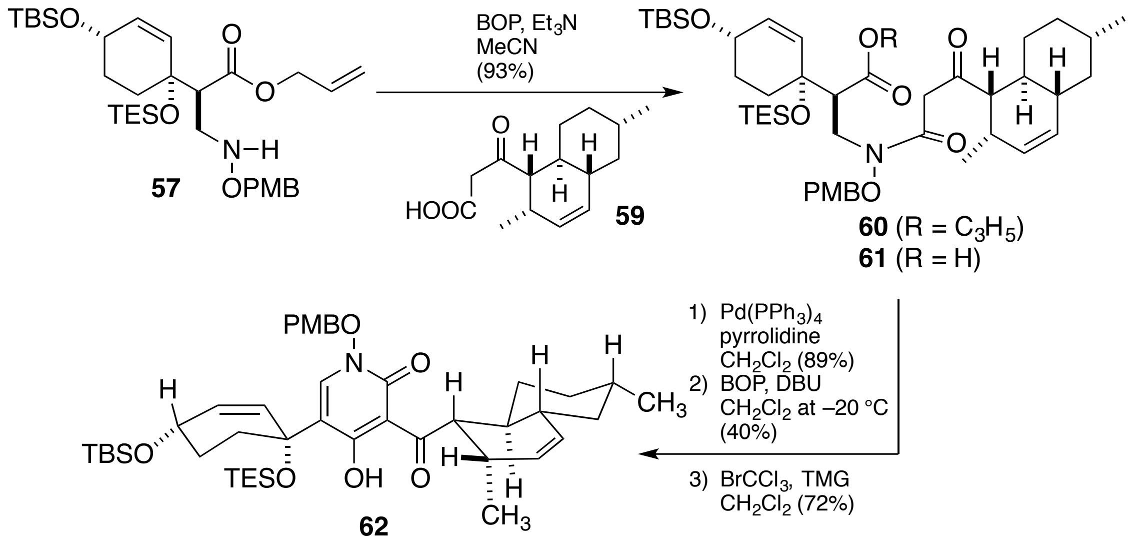
The enolate methodology of β-lactam **1** offers a valuable technique for providing access to the preparation of unique β-alanine (homoglycine) derivatives. By ring opening, these aldol products lead to an efficient synthesis of a variety of β-amino esters. Illustrations are shown in Scheme 3 using simple alcohols such as methanol and allyl alcohol to generate **55**, **56** and **57**, respectively. The formation of methyl esters from **29** and **43** (examples 1 and 2 of Scheme 3) are readily accomplished using methanol and potassium carbonate to achieve high yields of the respective esters without the need for protection of the secondary alcohol. Products **55** and **56** present an available amino function for further acylation. Example 3 (Scheme 3) demonstrates mild conditions for the incorporation of an alkoxide leading to the allyl ester **57**. We have also documented the *N*-acylation required for the synthesis of peptidomimetic substances as shown in the reaction of **29** to yield **58** via the incorporation of the *tert*-butyl ester of *L*-alanine. This directly provides an available β-amino group in **58** for further elaboration.

A significant goal of our studies sought to utilize our azetidin-2-ones for the preparation of β-amido esters as key intermediates for the construction of highly substituted 4-hydroxy-2-pyridinones. In fact, simple dihydropyridin-2-one derivatives have been obtained via the one-pot *N*-acylation of *N*-(4-methoxybenzyloxy)amine **57** upon treatment with diketene in CH_2Cl_2 followed by an intramolecular Claisen condensation in the presence of 4-dimethylaminopyridine (DMAP). This general concept is demonstrated in Scheme 4 for the synthesis of the complex 4-hydroxy-2-pyridinone **62**. In this case, the allyl ester **57** leads to amide **60** via *N*-acylation using the nonracemic carboxylic acid **59**[6] and benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP).[19] Deprotection of the allyl ester provides an unstable carboxylic acid **61**[20] for acyl activation (BOP, DBU) allowing for the ring closure to proceed at –20 °C. Subsequently, a mild oxidation with $BrCCl_3$ affords the 5-substituted-2-pyridinone **62**.[21,22] Our example shows that, *N*-acylations are feasible using the standard conditions that are compatible with demanding strategies for synthesis of peptidomimetics via these experiments.

Scheme 3. Transformations of Selected Azetidin-2-ones to Esters and Amides



Scheme 4. The Use of 1 in the Synthesis of 4-Hydroxy-2-pyridinones



CONCLUSION

In conclusion, our investigations have described aldol reactions using the reactive lithium enolate derived from *N*-(4-methoxybenzyloxy)-2-acetidinone (**1**) at –78 °C. Facile condensations with α,β-unsaturated enones and α-branched aldehydes produce good to excellent yields of 3-substituted-2-azetidinones. We have postulated that these reactions proceed via closed, six-membered transition states leading to *anti*-diastereoselection. Major adducts stemming from chiral, nonracemic α-substituted aldehydes feature three contiguous stereocenters corresponding to Felkin-Anh and *anti*-Felkin addition products. Unbranched aliphatic and aromatic or heteroaromatic aldehydes provide high yields of aldol products as mixtures of *anti*- and *syn*-diastereomers. Finally, we have illustrated opportunities for applications of these reactive β-lactams for the synthesis of complex substances containing C-linked β-amino acid derivatives, and further transformations produce C-5 substituted 4-hydroxy-pyridin-

2-ones. The aldol products derived from **1** may prove useful for the synthesis of novel peptidomimetics or C-linked glycopeptides via the incorporation of an unnatural β-alanine subunit. In this manner, the azetidinone **1** serves as a valuable β-homoglycine equivalent which allows for an efficient assembly of molecular complexity.

EXPERIMENTAL SECTION

General Methods. All reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon unless otherwise noted. All reagents and solvents were reagent grade and used as received with the following exceptions: Bulk grade hexanes and ethyl acetate (EtOAc) were distilled before use. Diethyl ether (Et_2O), tetrahydrofuran (THF), dimethylformamide (DMF), toluene, acetonitrile, and dichloromethane were degassed and passed through activated alumina columns in a commercial solvent purification system. Triethylamine (Et_3N), and pyridine were distilled from CaH_2 under dry air immediately before use. Allyl alcohol was distilled from magnesium turnings under Ar. Bromotrichloromethane ($BrCCl_3$) was distilled from CaH_2 under Ar. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and triethylsilyl trifluoromethanesulfonate (TESOTf) were distilled from CaH_2 under vacuum and stored under Ar. Dimethylsulfoxide (DMSO) was distilled from CaH_2 under vacuum and stored over 4Å molecular sieves under Ar. 1,1,3,3-Tetramethylguanidine (TMG) was distilled from BaO under Ar. Tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] was washed with degassed ethanol and degassed ether, then dried *in vacuo* overnight in the absence of light.[23] Commercial solutions of *n*-butyllithium (*n*-BuLi) were titrated with menthol in THF using 2,2′-bipyridine as an indicator. Commercial solutions of lithium 1,1,3,3-hexamethyldisilazane (LiHMDS) were titrated according to the method of Ireland.[24]

Dess–Martin periodinane (DMP) was prepared according to the literature procedure.[25] In addition to those defined above, the following reagents are referred to by their abbreviations: dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), and tetra-*n*-butylammonium fluoride (TBAF).

Reactions were monitored by analytical thin-layer chromatography (TLC) using glass-backed 0.25 mm thickness silica gel 60 (F_{254}) plates, which were visualized under UV light and/or by staining with ethanolic *p*-anisaldehyde. Preparative TLC was performed on 0.5 mm thickness 20 cm × 20 cm glass-backed silica gel 60 (F_{254}) plates. Flash chromatography was performed using silica gel 60 (230–400 mesh ASTM). Amounts of silica used are reported as volume (mL) of SiO_2. The sample was loaded as a solution in the minimum amount of the mobile phase, unless otherwise noted, and pressure was obtained using an airline bleed. Solvents were removed by rotary evaporation under aspirator vacuum, and all non-volatile samples were dried under high vacuum (0.1–0.2 mmHg) at rt.

Melting points were determined using a capillary melting point apparatus and are uncorrected. Optical rotations were obtained on a polarimeter at 589 nm (sodium D line) using a 10 cm path length and a 1.0 mL volume. Concentrations (*c*) are given in g/100 mL in the specified solvent. Infrared spectra are reported in wavenumbers (cm^{-1}). Oils were analyzed as films on sodium chloride plates; solids were analyzed on a diamond plate (ATR) or as films on sodium chloride plates. Proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were measured on 400 or 500 MHz spectrometers. The spectra were acquired as solutions in deuterated chloroform ($CDCl_3$), methanol (CD_3OD), or acetone ($(CD_3)_2CO$) and are reported in parts per million (δ, ppm) downfield using residual non-deuterated solvent as an internal standard set to δ 7.26, 3.23, and 2.05 for ^{1}H NMR and δ 77.16, 49.00, and 29.84 for ^{13}C NMR, respectively. ^{1}H NMR data are reported in the form: chemical shift (multiplicity, coupling constants, number of protons). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectral data (MS and HRMS) were recorded by use of electron impact (EI), fast atom bombardment (FAB) or electrospray ionization (ESI) with time-of-flight (TOF) analyzer. Data are reported in the form: *m*/z (relative intensity).

***N*-(4-Methoxybenzyloxy)azetidin-2-one (1).** *N*-(4-methoxybenzyloxy)amine (4.225 g, 27.58 mmol, 1 equiv) was dissolved in CH_2Cl_2 (92 mL, 0.3 M), cooled to 0 °C, and pyridine (2.35 mL, 29.05 mmol, 1.06 equiv) was added rapidly. To this clear, colorless solution was added 3-chloropropionyl chloride (2.80 mL, 29.3 mmol, 1.06 equiv) dropwise over 5 min. A white precipitate rapidly appeared, and then gradually disappeared before addition was complete, leaving a clear yellow solution. The cooling bath was removed and the reaction was allowed to warm to rt over 15 min. The reaction was diluted with pentane (200 mL), causing precipitation of a white solid. The yellow-white suspension was washed with water (1 x 50 mL), then 1 M HCl (1 x 10 mL), and the combined aqueous washes were extracted with CH_2Cl_2 (1 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 x 25 mL), saturated aqueous NaCl (1 x 25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a cream-colored solid. The crude material was purified by flash chromatography using diethyl ether to yield a thick oil. This oil was redissolved in CH_2Cl_2, an equal volume of

Et_2O was added, and then carefully concentrated *in vacuo* to precipitate 6.355 g (95%) of *N*-(4-methoxybenzyloxy)amide in a 2:1 mixture of amide rotamers as a fluffy white solid. This material could be recrystallized from CH_2Cl_2/hexanes, albeit in slightly reduced yields to give white crystals: mp 80–81 °C; R_f 0.1 [hexanes/EtOAc (2:1)]; IR (ATR) 3209 (br), 3031, 2952, 1653, 1607, 1515, 1238, 1033, 1014, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, br, 0.67H), 7.82 (s, br, 0.33H), 7.27–7.38 (m, br 2H), 6.88–6.96 (m, 2H), 4.88 (s, 1.33H), 4.77 (s, br, 0.67H), 3.82 (s, 3H), 3.80 (s, br, 2H), 2.82 (s, br, 0.67H), 2.49 (s, br 1.33H); ^{13}C NMR (101 MHz, $CDCl_3$ δ 173.5, 167.3, 160.2, 159.9, 131.0, 127.1, 126.1, 114.0, 113.8, 79.1, 77.8, 77.2, 55.2, 39.7, 38.5, 36.2, 34.6, 29.6; MS (FAB, NBA, Na^+) 244 (100), 209 (60), 195 (43), 151 (28), 137 (69); HRMS *m*/*e* $[M + H]^+$ calcd for $C_{11}H_{15}ClNO_3$ 244.0741, found 244.0744; Anal. calcd for $C_{11}H_{14}ClNO_3$ C 54.22, H 5.79, N 5.75, found C 54.17, H 5.77, N 5.68.

Sodium hydride (0.174 g of 60% dispersion in mineral oil, 4.36 mmol, 1.05 equiv) was slurried in DMF (1.4 mL) and cooled to 0 °C. A solution of the amide described above (1.01 g, 1 equiv) in DMF (4.0 mL) was added dropwise over 10 min with vigorous stirring. The reaction was stirred at 0 °C for 20 min, the cooling bath was removed, and the reaction was allowed to warm to rt over 10 min, during which time the suspension became a clear pale yellow solution. The reaction was then immersed in a pre-heated 60 °C oil bath and heated for 1 hr, during which time it became an opaque yellow suspension. Reaction progress was monitored by ^1H NMR spectroscopy (400 MHz, $CDCl_3$), and samples were prepared by filtration of a small aliquot through SiO_2 (1:1 hexanes/EtOAc) followed by concentration. The reaction was cooled to rt and then loaded directly onto a plug of silica, using small quantities of CH_2Cl_2 to aid transfer

(100% Et_2O). Following concentration, the wet, impure product was stirred under high vacuum for 4 hr to remove residual DMF resulting in a thick yellow oil. The crude material was purified by flash silica gel chromatography (100% Et_2O) to yield 0.506 g of a mixture of the desired β-lactam (**1**) containing small amounts of *N*-(4-methoxybenzyloxy)acrylamide (ratio 12:1). This viscous oil was purified by flash chromatography using diethyl ether, which led to crystallization of pure **1** upon concentration of the combined fractions as white needles (475 mg, 53% yield): mp 46–47 °C; R_f 0.33 [hexanes/EtOAc (1:1)], 0.45 (100% Et_2O); IR (neat) 3076, 3041, 3002, 2967, 1763, 1610, 1586, 1512, 1247, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ δ AB (δ_A = 7.32, δ_B = 6.89, J_{AB} = 8.7 Hz, 4H), 4.86 (s, 2H), 3.80 (s, 3H), 3.21 (t, J = 4.2 Hz, 2H), 2.61 (t, J = 4.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 160.1, 130.7, 127.2, 113.9, 77.3, 55.2, 44.9, 31.9; MS (CI/CH_4) 208 (1), 135 (19), 122 (45), 121 (100), 91 (27), 78 (33), 77 (39); HRMS *m/e* $[M + H]^+$ calcd for $C_{11}H_{14}NO_3$ 208.0974, found 208.0970; Anal. calcd for $C_{11}H_{13}NO_3$ C 63.76, H 6.32, N 6.76, found C 63.42, H 6.32, N 6.76.

(*R*)-3-[(1*S*,4*S*)-4-(*tert*-Butyldimethylsilanoxy)-1-hydroxycyclohex-2-enyl]-1-(4-methoxybenzyloxy)azetidin-2-one (8) and (*S*)-3-[(1*R*,4*S*)-4-(*tert*-Butyldimethyl-silanoxy)-1-hydroxycyclohex-2-enyl]-1-(4-methoxybenzyloxy)azetidin-2-one (9). To a –78 °C solution of β-lactam **1** (6.76 g, 32.6 mmol) in THF (326 mL) was added LiHMDS (27.4 mL of a 1.0 M solution in THF, 31.0 mmol) dropwise. The clear, yellow solution was stirred at –78 °C for 2 h, then a solution of ketone **7** (3.51 g, 15.5 mmol)[6] in THF (26 mL) was added dropwise. The reaction was stirred at –78 °C for 30 min, then it was quenched by the addition of saturated aqueous NH_4Cl (200 mL) and extracted with Et_2O

(2 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a yellow solid. NMR indicated a 1.2:1.0 ratio of **8:9**. The crude material was purified by flash chromatography (1 L SiO_2, 9:1 CH_2Cl_2–Et_2O) to provide alcohol **8** (3.55 g, 51%) and alcohol **9** (2.94 g, 44%), both as white solids.

For characterization of the major diastereomer **8**: mp 112–113 °C; R_f 0.28 [hexanes/EtOAc (1.5:1)], 0.2 [CH_2Cl_2/Et_2O (9:1)]; $[\alpha]^{22}_{D}$ –9.10 (*c* 0.714, $CHCl_3$); IR (film) 3420 (br), 3070, 2945, 2853, 1745, 1620, 1515, 1251, 1040, 875, 829, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (A of AB, J_{AB} = 7.34 Hz, 2H), 6.89 (B of AB, J_{BA} = 8.6 Hz, 2H), 5.74 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.39 (d, *J* = 10.2 Hz, 1H), 4.87 (A of AB, J_{AB} = 11.4 Hz, 1H), 4.87 (B of AB, J_{BA} = 11.4 Hz, 1H), 4.19 (dddd, *J* = 8.3, 3.3, 3.3, 1.6 Hz, 1H), 3.81 (s, 3H), 3.33 (dd, *J* = 4.3, 2.6 Hz, 1H), 3.23 (dd, *J* = 5.4, 4.4 Hz, 1H), 3.07 (dd, *J* = 5.4, 2.6 Hz, 1H), 2.21 (ddd, *J* = 13.1, 7.9, 2.6 Hz, 1H), 2.06 (br s, 1H), 1.96 (dddd, *J* = 13.0, 7.8, 4.9, 3.1 Hz, 1H), 1.71 (ddd, *J* = 13.6, 10.7, 2.9 Hz, 1H), 1.52 (dddd, *J* = 13.4, 10.2, 7.0, 3.1 Hz, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 160.1, 134.7, 130.9, 130.0, 127.2, 113.9, 77.5, 69.0, 65.8, 55.2, 52.9, 47.4, 32.4, 29.6, 25.8, 18.1, –4.6, –4.7; MS (CI) 416 (1), 376 (14), 122 (37), 121 (100), 73 (17); HRMS (EI) *m/z* $[M – OH]^+$ calcd for $C_{23}H_{34}NO_4Si$ 416.2257, found 416.2251; Anal. calcd for $C_{23}H_{35}NO_5Si$ C 63.71, H 8.14, N 3.23, found C 63.83, H 8.17, N 3.22.

For characterization of the minor diastereomer **9**: mp 73–75 °C; R_f 0.25 [hexanes/EtOAc (1.5:1)], 0.1 (9:1 CH_2Cl_2–Et_2O); $[\alpha]^{22}_{D}$ –27.9 (*c* 0.562, $CHCl_3$); IR (film) 3440 (br), 2932, 2846, 1759, 1614, 1581, 1508, 1258, 1093, 869, 829, 770 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.34 (A of AB, J_{AB} = 8.5 Hz, 2H), 6.89 (B of AB, J_{BA} = 8.5 Hz, 2H), 5.77 (d, *J* = 10.1 Hz, 1H), 5.41 (d, *J* = 10.1 Hz, 1H), 4.87 (A of AB, J_{AB} = 11.6 Hz, 1 H), 4.87 (B of AB, J_{BA} = 11.6 Hz, 1H), 4.12 (dddd, *J* = 8.5, 6.0, 2.0, 2.0 Hz, 1H), 3.81 (s, 3H), 3.26–3.19 (m, 2H), 2.95 (dd, *J* = 5.1, 2.5 Hz, 1H), 2.05 (br s, 1H), 2.02–1.95 (m, 1H), 1.86–1.77 (m, 1H), 1.71 (dddd, *J* = 12.4, 12.4, 9.0, 2.8 Hz, 1H), 1.58 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 160.1, 136.8, 130.9, 129.1, 127.2, 113.9, 77.5, 67.9, 67.2, 55.2, 53.9, 47.3, 32.0, 28.4, 25.8, 18.1, –4.6, –4.8; MS (CI) 416 (1), 197 (44), 122 (40), 121 (100), 105 (40), 75 (62), 73 (30); HRMS (EI) *m/z* $[M – OH]^+$ calcd for $C_{23}H_{34}NO_4Si$ 416.2257, found 416.2262; Anal. calcd for $C_{23}H_{35}NO_5Si$ C 63.71, H 8.14, N 3.23, found C 63.86, H 8.19, N 3.22.

General procedure for aldol reactions of Table 3 using β-lactam 1. To a –78 °C solution of β-lactam **1** (1.6 equiv) in THF (0.1 M) was added LiHMDS (2.0 equiv of a 1.0 M solution in THF) dropwise over 5 min. The clear, yellow solution was stirred at –78 °C for 2 h. Ketone or aldehyde substrate (1.0 equiv) was then added dropwise. The reaction was stirred at –78 °C for 15 to 30 min, or until the disappearance of the starting material by TLC. Reactions were quenched by the addition of saturated aqueous NH_4Cl or by pH 7 aqueous buffer, and extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Ratios were determined by the integration of selected ^1H NMR signals of the crude mixture of isomeric products, which were then purified by silica gel flash chromatography leading to spectroscopic characterizations of the major product diastereomers.

(*S*)-3-((1*S*,5*R*)-1-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-1-((4-methoxybenzyl)oxy)azetidin-2-one (21) (Table 3, entry 1). By application of the general procedure for the low temperature generation of the enolate of **1** (520 mg, 2.5 mmol), the reaction of (*R*)-carvone (180 mg, 1.2 mmol) in THF (25 mL; 0.1 M) gave the product lactam **21** as a colorless oil (385 mg, 90%), characterized a single diastereomer. R_f 0.78 [hexanes/EtOAc (6:4)]; $[\alpha]^{20}_{D}$ –51.0 (*c* 0.70, $CDCl_3$); IR (film) 3436, 3130, 2924, 1760, 1613, 1515, 1252, 1176, 1034, 821, 459 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2, Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.53–5.46 (m, 1H), 4.85 (q, *J* = 11.1 Hz, 2H), 4.73 (d, *J* = 12.6 Hz, 2H), 3.80 (s, 3H), 3.49 (dd, *J* = 4.3, 2.6 Hz, 1H), 3.25 (dd, *J* = 5.5, 4.3 Hz, 1H), 3.09 (dd, *J* = 5.5, 2.6 Hz, 1H), 2.35 (dt, *J* = 12.6, 2.2, 1H), 2.24 (dt, *J* = 15.1, 10.4 Hz, 1H), 2.12–2.05 (m, 2H), 1.94 (ddt, *J* = 17.9, 10.4, 2.2 Hz, 1H), 1.72 (d, *J* = 14.1 Hz, 3H), 1.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 160.1, 148.3, 135.7, 130.8, 127.3, 125.8, 113.9, 109.6, 77.5, 72.6, 55.3, 52.7, 48.3, 40.6, 38.5, 30.8, 20.8, 17.8; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{21}H_{27}NO_4Na$ 380.1838, found 380.1837.

3-(1-Hydroxy-2-methylpropyl)-1-(4-methoxybenzyloxy)azetidin-2-one (23) (Table 3, entry 2). Following the general procedure for the low temperature generation of the enolate of **1** (132 mg; 0.64 mmol), the aldehyde **22** (36.3 μL, 0.40 mmol) was introduced into the reaction at –78 °C. After stirring for 30 min, the reaction was quenched by the addition of aqueous NH_4Cl (6 mL) and extracted with ether (2 x 15 mL). Combined organic extracts were washed with aqueous $NaHCO_3$, then aqueous, saturated NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a thick oil. Flash silica gel chromatography using 40% EtOAc in hexanes afforded the crude product (109 mg, 0.39

mmol 97% yield) which proved to be principally one diastereomer (dr 94:6). Further purification by flash chromatography using 25% EtOAc in hexanes provided a pure sample of **23**. For characterization of the *anti*-diastereomer **23**: R_f 0.24 [hexanes/EtOAc (6:4)]; IR (film) 3470, 2962, 1756, 1612, 1515, 1253, 1033, 822, 559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.89 (A of AB, J_{AB} = 11.2 Hz, 1H), 4.86 (B of AB, J_{BA} = 11.2 Hz, 1H), 3.82 (s, 3H), 3.45 (td, *J* = 6.7, 3.3 Hz, 1H), 3.27 (t, *J* = 4.9 Hz, 1H), 3.10 (dd, *J* = 4.7, 2.5 Hz, 1H), 3.00 (ddd, *J* = 7.5, 5.3, 2.5 Hz, 1H), 2.38 (d, *J* = 3.5 Hz, 1H), 1.81–1.68 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 160.2, 130.9, 127.2, 114.0, 77.5, 75.6, 55.3, 48.9, 47.9, 33.1, 18.6, 17.8; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{21}NO_4Na$ 302.1368, found 302.1376.

3-[Cyclohexyl(hydroxy)methyl]-1-(4-methoxybenzyloxy)azetidin-2-one (25) (Table 3, entry 3). The aldol adduct **25** was prepared according to the general procedure for formation of the enolate from **1** (132 mg, 0.64 mmol) via introduction of aldehyde **24** (48.1 µl, 0.40 mmol) into the reaction at –78 °C. Flash chromatography[EtOAc/hexanes (4:6)] resulted in a pure sample of **25** from the crude product mixture (86%, 95:5 ratio of *anti–syn* isomers). A flash chromatograph of this product gave a sample of the pure diastereomer **25**: R_f 0.44 [hexanes/EtOAc (6:4)]; IR (film) 3478, 2928, 1744, 1612, 1516, 1252, 856, 550 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.87 (A of AB, J_{AB} = 11.3 Hz, 1H), 4.85 (B of AB, J_{BA} = 11.3 Hz, 1H), 3.81 (s, 3H), 3.45 (t, *J* = 6.7 Hz, 1H), 3.26 (t, *J* = 5.0 Hz, 1H), 3.10 (dd, *J* = 4.6, 2.6 Hz, 1H), 3.00 (ddd, *J* = 7.5, 5.2, 2.4 Hz, 1H), 2.45 (s, 1H), 1.85 (d, *J* = 13.0 Hz, 1H), 1.72 (m, 2H), 1.64 (d, *J* = 12.0 Hz, 1H), 1.57 (d, *J* = 12.6 Hz, 1H), 1.48–1.38 (m, 1H), 1.27–1.04 (m, 3H), 1.04–0.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 160.2, 130.9, 127.2, 114.0, 77.5, 74.9, 55.3, 54.1, 48.9, 47.8, 42.8, 28.8, 28.4, 26.3, 26.0, 25.8; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_4Na$ 342.1681, found 342.1666.

(*S*)-3-((*R*)-1-Hydroxy-3-methylcyclopent-2-en-1-yl)-1-((4-methoxybenzyl)oxy)azetidin-2-one (27) (Table 3, entry 4). Following the general procedure for the low temperature generation of the enolate of β-lactam **1** (124 mg; 0.60 mmol), the ketone **26** (28 mg, 0.29 mmol) was introduced into the reaction at –78 °C. After stirring for 30 min, the reaction was quenched by the addition of aqueous NH_4Cl (6 mL) and extracted with ether (2 x 8 mL). Combined organic extracts were washed with aqueous $NaHCO_3$, then aqueous, saturated NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a thick oil. Flash silica gel chromatography using diethylether afforded the crude product (63 mg, 72% yield) which proved to be principally the crude *anti*-adduct **27** containing small amounts of more polar *syn*-isomer (approximate dr 75:25). Rechromatography using Et_2O provided the pure *anti*-**27** (34 mg) which was characterized as follows: R_f 0.40 [Et_2O; 2 elutions]; IR (film) 3435, 2937, 1757, 1612, 1515, 1252, 1032, 822 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 2H), 6.95–6.84 (m, 2H), 5.20 (d, *J* = 1.7 Hz, 1H), 4.88 (d, *J* = 3.1 Hz, 2H), 3.82 (s, 4H), 3.26 (t, *J* = 5.2 Hz, 1H), 3.11 (m, 2H), 2.47–2.38 (m, 1H), 2.26–2.13 (m, 1H), 2.05 (dd, *J* = 8.8, 4.5 Hz, 1H), 1.96 (d, *J* = 4.5 Hz, 1H), 1.75 (t, *J* = 1.7 Hz, 3H) ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 160.1, 147.0, 130.8, 127.3, 127.0, 114.0, 84.4, 77.7, 55.3, 53.2, 48.1, 37.4, 35.3, 16.8; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{21}O_4NNa$ 326.1368, found 326.1364.

A pure sample of the minor product (3.0 mg) was characterized as the corresponding *syn*-isomer **27a**: R_f 0.45 [Et_2O; 2 elutions]; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 2H), 6.95–6.84 (m, 2H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.88 (d, *J* = 3.1 Hz, 2H), 3.82 (s, 3H), 3.29 (t, *J* = 5.2 Hz, 1H), 3.11 (m, 2H), 2.47–2.38 (m, 1H), 2.26–2.13 (m, 1H), 2.10–2.07 (m, 1H), 1.97 (d, *J* = 4.7 Hz, 1H), 1.75 (t, *J* = 1.2 Hz, 3H). Small quantities of **27a** proved insufficient for ^{13}C NMR analysis. HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{21}O_4NNa$ 326.1368, found 326.1367.

(*R*)-3-((*S*)-((2*R*,3*S*,4*S*)-3-(Benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)tetrahydrofuran-2-yl)(hydroxy)methyl)-1-(4-methoxybenzyloxy)azetidin-2-one (29) (Table 3, entry 5). Following the general procedure for the low temperature generation of the enolate of **1** (50 mg, 0.24 mmol), aldehyde **28** (69 mg, 0.15 mmol) was introduced into the reaction at –78 °C. After stirring for 40 minutes, the reaction was quenched by the addition of aqueous pH 7 buffer (10 mL) and extracted with Et_2O (2 x 8 mL). Combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a thick, colorless oil. An initial flash chromatography using Et_2O provided three product diastereomers (90 mg; dr 76:18:7) in approximately 90% yield. A subsequent flash chromatography (10% EtOAc in CH_2Cl_2) gave 60 mg of the major product **29**, and additional fractions of inseparable mixtures (total 20 mg) that contained the minor *anti*-adduct together with a small amount of an uncharacterized *syn*-isomer (ratio 2:1). The major azetidinone *anti*-**29** was characterized as follows: R_f 0.66 [EtOAc/CH_2Cl_2 (1:9)]; IR (film) 3443, 3070, 2933, 1756, 1612, 1515, 1252, 1112, 1076, 823, 735, 702, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dt, *J* = 6.5, 1.6 Hz, 2H), 7.67–7.60 (dt, *J* = 6.5, 1.6 Hz, 2H), 7.50–7.37

(m, 6H), 7.34–7.22 (m, 5H), 7.07 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.89–6.82 (m, 2H), 4.85 (d, *J* = 2.9 Hz, 2H), 4.31 (d, *J* = 3.7 Hz, 1H), 4.16 (dd, *J* = 8.1, 3.7 Hz, 1H), 4.06–3.95 (m, 4H), 3.90 (dd, *J* = 9.5, 3.9 Hz, 1H), 3.78 (s 3H), 3.74 (dd, *J* = 9.5, 1.2 Hz, 1H), 3.28 (d, *J* = 4.0 Hz, 2H), 3.14 (dt, *J* = 6.2, 4.0 Hz, 1H), 2.71 (d, *J* = 4.4 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 160.1, 137.6, 135.9, 135.7, 133.2, 130.9, 130.1, 130.0, 128.4, 127.9, 127.9, 127.8, 127.5, 127.3, 113.9, 84.8, 81.6, 77.5, 75.9, 74.3, 71.6. 68.1, 55.2 48.5, 48.4, 26.9, 19.0; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{39}H_{45}NO_7NaSi$ 690.2863, found 690.2871.

(*S*)-3-((1*S*,2*R*,3*S*)-3-((Benzyloxy)methoxy)-1-hydroxy-2-methylbutyl)-1-((4-methoxybenzyl)oxy)azetidin-2-one (31) (Table 3, entry 6). Following the general procedure for the low temperature generation of the enolate of β-lactam **1** (50 mg, 0.24 mmol), the aldehyde **30** (33 mg, 0.15 mmol) was introduced into the reaction at –78 °C. After stirring for 40 min, the reaction was quenched by the addition of aqueous NH_4Cl (5 mL) and extracted with ether (2 x 8 mL). Combined organic extracts were washed with aqueous $NaHCO_3$, then aqueous, saturated NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a viscous oil. Flash silica gel chromatography using Et_2O provided two *anti*-products (61 mg; dr 75:25) in 94% yield. These two diastereomeric adducts were separated via flash chromatography using Et_2O leading to the isolation of the major component (37 mg) which was characterized as the *anti*-isomer **31**: R_f 0.40 [EtOAc/CH_2Cl_2 (3:7)]; IR (film) 3475, 2930, 1759, 1612, 1514, 1252, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.13 (m, 7H), 6.83–6.76 (m, 2H), 4.78 (s, 2H), 4.71 (d *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.51 (s, 2H), 4.03 (dt, *J* = 5.6, 2.5 Hz, 1H), 3.70 (m, 4H), 3.16 (q, *J* = 3.6, 2.4 Hz, 1H), 2.94–2.90 (m, 1H), 2.80 (d, *J* = 3.6 Hz. 1H), 1.35

(pd, J = 7.1, 2.5 Hz, 1H), 1.12 (d, J = 5.6 Hz, 3H), 0.84 (d, J = 7.1 Hz. 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 160.1, 137.6, 130.9, 128.5, 127.8, 127.8, 127.3, 114.0, 93.8, 77.5, 76.5, 69.9, 69.8, 57.2, 55.2, 48.5, 43.0, 18.5, 10.4; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{31}NO_6Na$ 452.2049, found 452.2033.

(*S*)-3-[(1*S*,2*R*)-3-(*tert*-Butyldiphenylsilanoxy)-1-hydroxy-2-methylpropyl]-1-(4-methoxybenzyloxy)azetidin-2-one (33) and (*R*)-3-[(1*R*,2*R*)-3-(*tert*-butyldiphenylsilanoxy)-1-hydroxy-2-methylpropyl]-1-(4-methoxybenzyloxy)-azetidin-2-one (33a) (Table 3, entry 7). Following the general procedure for the low temperature generation of the enolate of β-lactam **1** (124 mg, 0.60 mmol), the aldehyde **32** (130 mg, 0.40 mmol) was introduced into the reaction at –78 °C. After stirring for 30 minutes, the reaction was quenched by the addition of aqueous NH_4Cl (5 mL) and extracted with ether (2 x 10 mL). Combined organic extracts were washed with aqueous $NaHCO_3$, then saturated aqueous NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a viscous oil. Flash silica gel chromatography using 50% EtOAc in hexanes provided two products (178 mg, dr 58:42) as diastereomers in 80% yield, which were separated via flash chromatography (30% EtOAc in hexanes). The more polar, major product (95 mg) was characterized as the *anti*-isomer **33**: R_f 0.18 [hexanes/EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4 H), 7.47–7.27 (m, 8 H), 6.89 (d, J = 8.4 Hz, 2H), 4.88 (s, 2H), 3.98 (dt, J = 7.6, 3.8 Hz, 1H), 3.80 (s, 3H), 3.70 (A of ABX, J_{AB} = 10.3 Hz, J_{AX} = 6.6 Hz, 1H), 3.63 (B of ABX, J_{BA} = 10.3 Hz, J_{BX} = 4.6 Hz, 1H), 3.24 (t, J = 4.9 Hz, 1H), 3.08–3.02 (m, 2H), 2.78 (d, J = 4.0 Hz, 1H), 1.75–1.66 (m, 1H), 1.05 (s, 9H), 0.91 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 160.1, 135.6, 133.1, 130.9, 129.8, 127.7, 127.3, 114.0, 77.5, 71.8, 68.2, 66.6, 55.3, 48.5, 39.6, 26.9, 19.2, 10.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{31}H_{40}NO_5Si$ 534.2676, found 534.2695.

The minor product (75 mg) was characterized *anti*-adduct **33a**: R_f 0.22 [hexanes/EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.47–7.32 (m, 8H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.90 (s, 2H), 3.92 (t, *J* = 2.1 Hz, 1H), 3.80 (s, 3H), 3.80–3.72 (m, 2H), 3.59 (dd, *J* = 10.1, 8.2 Hz, 1H), 3.39 (dd, *J* = 4.0, 2.4 Hz, 1H), 3.25 (t, *J* = 4.9 Hz, 1H), 3.10 (td, *J* = 5.0, 2.3 Hz, 1H), 2.23–2.14 (m, 1H), 1.05 (s, 9H), 0.80 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 160.1, 135.5, 133.4, 130.9, 129.8, 127.7, 127.3, 114.0, 77.5, 71.8, 66.6, 58.5, 55.3, 48.3, 39.6, 26.9, 19.2, 10.9; HRMS (ESI-TOF) *m/z* calcd for $C_{31}H_{40}NO_5Si$ $(M+H)^+$ 534.2676, found 534.2682. The absolute stereochemistry of the secondary alcohol in **33** and **33a** was determined using the modified Mosher analysis[18a] of each isomer which identified the stereotriad present in these *anti*-adducts. The Mosher analyses are summarized in the Supporting Information.

(*S*)-3-[(1*S*,2*R*)-2-(Benzyloxy)-1-[hydroxypropyl]-1-(4-methoxybenzyloxy)azetidin-2-one (35) and (*R*)-3-[(1*S*,2*S*)-2-(benzyloxy)-1-hydroxypropyl]-1-(4-methoxybenzyloxy)azetidin-2-one (35a) (Table 3, entry 8). The aldol adducts **35** and **35a** were prepared according to the general procedure (81%, 80:20 *anti–syn*, *anti*-ratio dr 65:35 for **35**:**35a**). Major diastereomer **35** was difficult to separate from an inseparable mixture *syn*-isomers and an unidentified impurity. After repeated purifications by flash chromatography, a sample of **35** was obtained for characterization. R_f 0.42 [CH_2Cl_2/Et_2O (9:1)]; IR (film) 3440 (br), 3041, 2962, 1755, 1610, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 7H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.87 (s, 2H), 4.60 (A of AB, J_{AB} = 11.5 Hz, 1H), 4.44 (B of AB, J_{BA} = 11.5 Hz, 1H), 3.81 (s, 3H), 3.65

(t, *J* = 6.8 Hz, 1H), 3.55 (t, *J* = 6.3 Hz, 1H), 3.27 (t, *J* = 5.1 Hz, 1H), 3.22–3.19 (m, 1H), 3.12 (qd, *J* = 5.2, 2.5 Hz, 1H), 1.24 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$ δ 165.4, 157.2, 138.2, 130.9, 128.5, 128.4, 127.7 (2), 114.0, 77.5, 77.4, 73.7, 71.1, 55.3, 49.0, 47.3, 15.9; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{21}H_{25}NO_5Na$ 394.1630, found 394.1613.

The minor products that are assigned as the *syn*-diastereomers were inseparable and were not individually characterized. However, the minor *anti*-diastereomer was less polar and was readily separated by flash chromatography using 10% ether in methylene chloride. The minor *anti*-isomer **35a** was characterized as follows: R_f 0.60 [CH_2Cl_2/Et_2O (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 7H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.88 (s, 2H), 4.64 (A of AB, J_{AB} = 11.4 Hz, 1H), 4.44 (B of AB, J_{BA} = 11.4 Hz, 1H), 3.81 (s, 3H), 3.77 (quintuplet, *J* = 6.2 Hz, 1H), 3.66 (t, *J* = 5.7 Hz, 1H), 3.31 (dd, *J* = 4.4, 2.5 Hz, 1H), 3.22 (t, *J* = 5.0 Hz, 1H), 3.04 (td, *J* = 5.2, 2.5 Hz, 1H), 2.89 (br s, 1H), 1.21 (d, *J* = 6.1 Hz, 3H); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{21}H_{25}NO_5Na$ 394.1630, found 394.1626.

(*S*)-3-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-2-phenylethyl)-1-((4-methoxybenzyl)oxy)azetidin-2-one (37) (Table 3, entry 9). Following the general procedure for enolate formation of **1** (132 mg, 0.64 mmol), the aldehyde **36** (93.8 mg, 0.40 mmol) was introduced into the reaction at –78 °C. After stirring for 30 minutes, the reaction was quenched by the addition of aqueous pH 7 buffer (5 mL), and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with saturated, aqueous NaCl (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a viscous oil. An initial flash chromatography using 40% EtOAc in hexanes provided a mixture of two product diastereomers (dr 53:47) in 80% yield and the recovery of starting β-lactam (**1**) (45 mg). Subsequent gradient flash chromatography using EtOAc in hexanes (6.6% to 20% EtOAc in hexanes by volume) gave the less polar product (65 mg) which was characterized as *anti*-**37**: R_f 0.88 [hexanes/EtOAc (6:4)]; IR (film) 3480, 3034, 2955, 1770, 1613, 1515, 1253, 1062, 837, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 7H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.83 (d, *J* = 2.5 Hz, 2H), 4.77 (d, *J* = 5.9 Hz, 1H), 3.82 (s, 3H), 3.72 (m, 1H), 3.22 (ddd, *J* = 7.4, 5.2, 2.4 Hz, 1H), 3.07 (dd, *J* = 5.0, 5.2 Hz, 1H), 2.62 (dd, *J* = 5.0, 2.4 Hz, 1H), 2.28 (d, *J* = 3.8 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), –0.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 160.1, 141.1, 130.9, 128.2, 127.9, 127.1, 126.5, 113.9, 77.4, 76.4, 75.4, 55.2, 48.8, 45.6, 25.8, 18.1, –4.8; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{35}NO_5Si$ 480.2177, found 480.2164.

The minor *anti*-diastereomer **37a** was characterized as follows: R_f 0.81 [hexanes/EtOAc (6:4)]; IR (film) 3442, 3032, 2955, 1758, 1612, 1515, 1253, 1060, 779, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 7H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.85 (d, *J* = 2.5 Hz, 2H), 4.77 (d, *J* = 5.9 Hz, 1H), 3.82 (s, 3H), 3.72 (dt, *J* = 5.9, 7.3 Hz, 1H), 3.22 (ddd, *J* = 7.3, 5.0, 2.5 Hz, 1H), 3.08 (t, *J* = 5.0 Hz, 1H), 2.62 (dd, *J* = 5.0, 2.5 Hz, 1H), 2.21 (s, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 160.1, 141.1, 130.9, 128.3, 127.9, 127.2, 126.6, 113.9, 77.4, 76.4, 75.5, 55.2, 48.8, 45.6, 25.8, 18.1, –4.8, –4.9; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{35}NO_5Si$ 480.2177, found 480.2182.

(*R*)-3-((*R*,*E*)-1-Hydroxy-3-phenylallyl)-1-((4-methoxybenzyl)oxy)azetidin-2-one (39) (Table 3, entry 10). Following the general procedure for the low temperature generation of solutions of the enolate of **1** (100 mg, 0.48 mmol) utilizing LiHMDS (0.45

mL of 1M solution) in THF, aldehyde **38** (40 mg, 0.30 mmol) was introduced into the reaction mixture at –78 °C. After stirring for 20 minutes, the reaction was quenched by the addition of aqueous pH 7 buffer (8 mL), and extracted with Et_2O (2 x 10 mL). Combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a viscous oil. An initial flash chromatography using 20% EtOAc in CH_2Cl_2 provided the mixture of *anti*- and *syn*-diastereomers (100 mg; dr 78:22) in 98% yield. Subsequent flash chromatography [EtOAc/hexanes (1:5)] afforded pure samples leading to isolation and characterization of the major product as *anti*-**39**: R_f 0.45 [EtOAc/CH_2Cl_2 (1:5)]; IR (film) 3414, 2962, 1754, 1612, 1514, 1252, 1032, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 7H), 6.89–6.85 (m, 2H), 6.63–6.56 (d, *J* = 15.9, 1H), 6.23 (dd, *J* = 15.9, 6.9 Hz, 1H), 4.88 (s, 2H), 4.49 (td, *J* = 6.9, 2.2 Hz, 1H), 3.81 (s, 3H), 3.28 (t, *J* = 4.9 Hz, 1H), 3.17–3.10 (m, 2H), 2.24 (d, *J* = 3.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 160.2, 135.9, 132.5, 130.9, 128.6, 128.2, 127.7, 127.2, 126.7, 114.0, 77.7, 71.3, 55.3, 50.2, 47.9; HRMS (ESI-TOF) *m/z* $[M + Na]^+$calcd for $C_{20}H_{21}NO_4Na$ 362.1368, found 362.1353.

For characterization of the minor product as *syn*-**39a**: R_f 0.50 [EtOAc/CH_2Cl_2 (1:5)]; IR (film) 3411, 2963, 1755, 1612, 1514, 1252, 1032, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 7.32–7.21 (m, 2H), 6.92–6.83 (m, 2H). 6.63 (dd, *J* = 15.9, 1.4 Hz, 1H), 6.16 (dd, *J* = 15.9, 5.9 Hz, 1H), 4.89 (d, *J* = 1.6 Hz, 2H), 4.67 (m, 1H), 3.81 (s, 3H), 3.38 (dd, *J* = 4.6, 2.5 Hz, 1H). 3.27 (dd, *J* = 4.5, 5.2 Hz, 1H), 3.12 (ddd, *J* = 5.2, 4.5, 2.5 Hz, 1H), 2.08–2.01 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 160.2, 136.0. 131.4, 130.9. 128.6, 128.2, 128.0, 127.2, 126.6, 114.0, 77.6, 68.8, 55.3, 50.6, 47.0; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{20}H_{21}NO_4Na$ 362.1368, found 362.1361.

3-[Hydroxy(phenyl)methyl]-1-(4-methoxybenzyloxy)azetidin-2-one (41) (Table 3, entry 11). Following the general procedure for low temperature generation of the enolate from **1** (133 mg, 0.64 mmol), benzaldehyde (41 µL, 0.40 mmol) was introduced into the reaction at –78 °C. After stirring for 30 min, the reaction was quenched by the addition of aqueous NH_4Cl (6 mL) and extracted with ether (2 x 15 mL). Combined organic extracts were washed with aqueous $NaHCO_3$, then aqueous, saturated NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a thick oil. Flash silica gel chromatography using 30% EtOAc in hexanes afforded the crude product (117 mg, 93% yield) which proved to be a mixture of two diastereomers (dr 80:20). The major product **41** (89 mg) was obtained as a pure sample following flash chromatography using 35% EtOAc in hexanes, and was characterized by the following data: R_f 0.44 [hexanes/EtOAc (6:4)]; IR (film) 3410, 3033, 2958, 1755, 1612, 1515, 1252, 1032, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 7.21 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.88 (d, J = 7.0 Hz, 1H), 4.75 (A of AB, J_{AB} = 11.0 Hz, 1H), 4.69 (B of AB, J_{BA} = 11.0 Hz, 1H), 3.80 (s, 3H), 3.42 (s, 1H), 3.25 (ddd, J = 6.7, 5.2, 2.3 Hz, 1H), 3.18 (t, J = 5.1 Hz, 1H), 3.02 (dd, J = 4.9, 2.3 Hz, 1H); ^{13}C NMR (127 MHz, $CDCl_3$) δ 164.7, 160.1, 140.6, 130.9, 128.5, 128.2, 127.1, 126.4, 114.0, 77.6, 72.3, 55.3, 51.5, 48.0; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{19}NO_4Na$ 336.1212, found 336.1208.

3-[Furan-2-yl(hydroxy)methyl]-1-(4-methoxybenzyloxy)azetidin-2-one (43) (Table 3, entry 12). Following the general procedure for the low temperature generation of the enolate of β-lactam **1** (373 mg, 1.80 mmol), furfural (**42**: 86.9 µL, 1.00 mmol) was introduced into the reaction at –78 °C. After stirring for 60 min, the reaction was quenched by the addition of aqueous NH_4Cl (20 mL) and extracted with ether (2 x 15 mL). Combined organic extracts were washed with aqueous $NaHCO_3$, then aqueous, saturated NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a thick oil. Flash silica gel chromatography using 50% EtOAc in hexanes afforded the crude product (281 mg, 93% yield) as a mixture of two diastereomers (dr 83:17). Flash chromatography of this mixture [CH_2Cl_2/ether (9:1)] led to the isolation of 248 mg (82% of the major product which was determined to be the *anti*-diastereomer **43** and was fully characterized as follows: R_f 0.22 [hexanes/EtOAc (1:1)]; IR 3483, 2969, 2900, 1749, 1612, 1515, 1255, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 0.8 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.34 (d, *J* = 3.1 Hz, 1H), 6.31 (d, *J* = 3.1 Hz, 1H), 4.87 (d, *J* = 7.0 Hz, 1H), 4.82 (s, 2H), 3.79 (s, 3H), 3.34 (ddd, *J* = 6.9, 5.1, 2.3 Hz, 1H), 3.28 (t, *J* = 5.0 Hz, 1H), 3.25 (br s, 1H), 3.15 (dd, *J* = 4.7, 2.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 160.2, 153.5, 142.5, 131.0, 127.1, 114.1, 110.5, 107.5, 77.7, 66.3, 55.4, 49.3, 48.4; MS (FAB) 362 (17), 121 (100), 107 (46); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{17}NO_5Na$ 326.1004, found 326.1013.

The minor product (33 mg) was characterized as the *syn*-diastereomer **43a**: R_f 0.31 [hexanes/EtOAc (1:1)]; IR 3403, 2925, 1760, 1612, 1515, 1253, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 3H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.23 (d, *J* = 3.3 Hz, 1H), 5.10 (s, 1H), 4.88 (A of AB, J_{AB} = 11.1 Hz, 1H), 4.86 (B of AB, J_{BA} = 11.1 Hz, 1H), 3.81 (s, 3H), 3.61–3.59 (m, 1H), 3.32 (t, *J* = 5.1 Hz, 1H), 3.30 (dd, *J* = 4.3, 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 160.2, 154.1, 142.5, 131.1, 127.3, 114.1, 110.4, 107.0, 77.7, 63.5, 55.4, 49.4, 47.1; MS (FAB) 362 (1), 299 (15), 279, (20), 121 (100); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{17}NO_5Na$ 326.1004, found 326.1016.

3-(1-Hydroxypropyl)-1-(4-methoxybenzyloxy)azetidin-2-one (45) (Table 3, entry 13). The aldol adducts were prepared according to the general procedure (80%, dr 88:12 *anti–syn*). Major diastereomer **45**: R_f 0.20 [hexanes/EtOAc (6:4)]; IR (film) 3443, 2958, 1752, 1612, 1515, 1253, 984, 820, 536 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.86 (s, 2H), 3.80 (s, 3H), 3.76–3.71 (m, 1H), 3.26 (t, J = 5.0 Hz, 1H), 3.12 (dd, J = 4.6, 2.5 Hz, 1H), 2.92 (ddd, J = 6.2, 5.4, 2.5 Hz, 1H), 2.33 (br s, 1H), 1.61–1.72 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 160.2, 130.9. 127.2, 114, 77.5, 69.8, 55.3, 50.3, 48.2, 37.6, 18.6, 13.8; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{21}NO_4Na$ 302.1368, found 302.1376.

3-[4-(*tert*-Butyldimethylsilanoxy)-1-hydroxybutyl]-1-(4-methoxybenzyloxy)azetidin-2-one (47) (Table 3, entry 14). Following the general procedure for the low temperature generation of the enolate of **1** (132 mg, 0.64 mmol), the aldehyde **46** (131 mg, 0.40 mmol) was introduced into the reaction at –78 °C. After stirring for 30 min, the reaction was quenched by the addition of aqueous NH_4Cl (6 mL) and extracted with ether (2 x 15 mL). Combined organic extracts were washed with aqueous $NaHCO_3$, then aqueous, saturated NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a thick oil. Flash silica gel chromatography using EtOAc in hexanes [gradient of 20% EtOAc/hexanes to 30% EtOAc/ hexanes] afforded the crude product (187 mg, 87% yield), which proved to be two diastereomers (dr 89:11). Flash chromatography using 20% EtOAc in hexanes gave a pure sample of the major adduct (96 mg) which was characterized as *anti*-**47**: R_f 0.37 [hexanes/EtOAc (6:4)]; IR (film) 3426, 2897, 1758, 1515, 1252, 1112, 704, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 6.0 Hz, 4H), 7.46–7.32 (m, 8 H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.88 (s, 2H), 3.80 (s, 3H), 3.69 (t, *J* = 5.0 Hz, 2H), 3.27 (t, *J* = 5.0 Hz, 1H), 3.18 (dd, *J* = 4.6, 2.4 Hz, 1H), 2.96 (td, *J* = 5.5, 2.4 Hz, 1H), 2.89 (d, *J* = 4.3 Hz, 1H), 1.74–1.60 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 160.2 135.5, 133.4, 130.9, 129.7, 127.7, 127.3, 113.9, 77.5, 69.5, 63.9, 55.3, 50.4, 48.1, 32.2, 28.6, 26.8, 19.1; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{31}H_{39}NO_5SiNa$ 556.2495, found 556.2506.

(*S*)-3-((1*R*,5*S*,7*S*)-7-(Bromomethyl)-4,7-dimethyl-6-oxabicyclo[3.2.1]oct-3-en-5-yl)-1-((4-methoxybenzyl)oxy)azetidin-2-one (48). To a solution of the β-lactam **21** (20 mg, 0.056 mmol) in THF (0.6 mL) was added *N*-bromosuccinimide (15 mg, 0.084 mmol, 1.5 equiv). After 1 hour the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 x 1 mL). The combined organic layer was washed with saturated aqueous $NaHSO_3$, brine, and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (40% EtOAc in hexanes) furnished bromide **48** as a white solid (18 mg, 73% yield): R_f 0.70 [hexanes/EtOAc (6:4)]; IR (film) 3070, 2933, 1730, 1513, 1249, 1111, 703 cm^{-1}; $[\alpha]^{20}_{D}$ +13.2 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (d, *J* = 8.6 Hz, 2H), 6.94–6.82 (d, *J* = 8.6 Hz, 2H), 5.32 (s, 1H), 4.95–4.80 (m, 2H), 3.82 (s, 3H), 3.43 (d, *J* = 10.0 Hz, 1H), 3.34 (m, 3H), 3.20 (dd, *J* = 5.0, 3.0 Hz, 1H), 2.63 (dd, *J* = 11.1, 5.1 Hz, 1H), 2.47 (d, *J* = 19.1 Hz, 1H), 2.37 (d, *J* = 5.1 Hz, 1H), 2.34–2.24 (d, *J* = 19.1 Hz, 1H), 1.81 (d, *J* = 11.1 Hz, 1H), 1.60 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 160.1, 140.1, 130.9, 127.4, 123.2, 113.9, 85.3, 80.3, 77.5, 55.2, 48.7, 48.5, 41.4, 38.3, 36.0, 29.6, 26.0, 18.8; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{21}H_{26}BrNNaO_4$ 458.0937, found 458.0927 (M) and 460.0906 (M + 2 bromine isotope).

Methyl-(2*R*,3*S*)-3-((2*R*,3*S*,4*S*)-3-(benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)tetrahydrofuran-2-yl)-3-hydroxy-2-((((4-methoxybenzyl)oxy)amino)methyl)propanoate (55). A reaction vial is charged with β-lactam **29** (29 mg, 0.043 mmol) in methanol (1 mL), and K_2CO_3 (9 mg) is added. The suspension is stirred at 22 °C for 30 min, and then is concentrated under reduced pressure. The crude product is applied to a pipette column of silica gel and eluted with 10% EtOAc in methylene chloride. After removal of solvents *in vacuo*, the desired methyl ester **55** (28 mg, 93% yield) is isolated as a clear oil: R_f 0.60 [EtOAc/CH_2Cl_2 (1:9)]; IR (film) 3420, 2931, 2857, 1712, 1649, 1248, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.60 (m, 4H), 7.49–7.36 (m, 6H), 7.29–7.20 (m, 5H), 7.10 (m, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.91 (s, 1H), 4.60 (s, 2H), 4.34–4.29 (m, 1H), 4.15 (m, 2H), 4.07 (q, *J* = 11.9 Hz, 2H), 3.93 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.88 (d, *J* = 2.3 Hz, 1H), 3.78 (s, 4H), 3.73 (s, 3H), 3.44 (d, *J* = 5.2 Hz, 1H), 3.34 (dd, *J* = 6.3, 4.2 Hz, 2H), 3.18 (td, *J* = 6.3, 2.0 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 159.3, 137.9, 135.8, 135.7, 133.3, 133.2, 130.1, 130.1, 130.0, 129.7, 128.3, 127.9, 127.8, 127.6, 127.3, 113.7, 84.4, 81.1, 76.0, 75.7, 74.4, 71.9, 69.7, 55.2, 52.3, 51.7, 45.8, 26.9, 19.1; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{40}H_{50}NO_8Si$ 700.3306, found 700.3320.

Methyl-(2*R*,3*S*)-3-(furan-2-yl)-3-hydroxy-2-(4-methoxybenzyloxy)aminomethylpropanoate (56). A flask is charged with β-lactam **43** (36 mg, 0.119 mmol) in methanol (1.2 mL) and K_2CO_3 (25 mg, 0.179 mmol) is added. The suspension is stirred at 22 °C for 30 minutes, and then is diluted with water (8 mL). After extraction with ether (3 x 5 mL), the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Upon flash silica gel chromatography (hexanes/EtOAc, 1:1 by volume), the desired methyl ester **56** (35 mg) is isolated as a white solid (87% yield) which was characterized as follows: R_f 0.55 [hexanes/EtOAc (1:1)]; IR (film) 3504, 3277, 3148, 1730, 1513, 1248, 1174, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.32–7.19 (m, 2H), 6.92–6.80 (m, 2H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.26 (dt, *J* = 3.3, 0.8 Hz, 1H), 5.66 (s, NH, 1H), 5.00 (d *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.30 (dt, *J* = 6.9, 5.9 Hz. 1H), 3.22 (dd, *J* = 13.3, 6.9 Hz, 1H), 3.14 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.16–3.09 (m, OH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 159.3, 154.0, 142.1, 130.0, 129.3, 113.6, 110.1, 107.0, 75.7, 67.6, 55.1, 51.9, 51.0, 48.0; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{21}NO_6Na$ 358.1261, found 358.1259.

Allyl (*S*)-2-[(1*R*,4*S*)-4-(*tert*-butyldimethylsilanoxy)-1-(triethylsilanoxy)-cyclohex-2-enyl]-3-(4-methoxybenzyloxyamino)propionate (57). To a 0 °C solution of the β-lactam **9** (679 mg, 1.57 mmol) in CH_2Cl_2 (16 mL) was added pyridine (190 µL, 2.35 mmol) dropwise, followed by TESOTf (425 µL, 1.88 mmol) dropwise. The clear, colorless solution was stirred at 0 °C for 5 min, becoming cloudy white, then it was stirred at rt for 10 min. The reaction was diluted with pentane (32 mL) and H_2O (16 mL) and stirred vigorously until all of the solids dissolved. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*, removing traces of pyridine under high vacuum. The crude material was purified by flash chromatography [hexanes/EtOAc (6:1)] to provide the TES silyl ether of **9** (822 mg, 96%) as a white solid: mp 79.5–81.5 °C; R_f 0.68 [hexanes/EtOAc (1.5:1)]; $[\alpha]^{22}_{D}$ –89 (*c* 0.51, $CHCl_3$); IR 3056, 3031, 2943, 1758, 1610, 1581, 1512, 1252, 1060, 976, 839, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.33 (A of AB, J_{AB} = 8.6 Hz, 2H), 6.89 (B of AB, J_{BA} = 8.6 Hz, 2H), 5.66 (dd, J = 10.1, 4.0 Hz, 1H), 5.43 (d, J = 10.1 Hz, 1H), 4.90 (A of AB, J_{AB} = 11.0 Hz, 1H), 4.83 (B of AB, J_{AB} = 11.0 Hz, 1H), 4.05 (q, J = 4.1 Hz, 1H), 3.81 (s, 3H), 3.42 (dd, J = 3.9, 2.6 Hz, 1H), 3.17 (dd, J = 5.4, 4.2 Hz, 1H), 2.94 (dd, J = 5.3, 2.3 Hz, 1H), 2.2–2.0 (m, 2H), 1.78–1.64 (m, 2H), 0.93 (t, J = 7.9 Hz, 9H), 0.88 (s, 9H), 0.68–0.52 (m, 6H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 160.0, 133.2, 131.8, 130.6, 127.5, 113.9, 77.3, 71.0, 64.1, 55.2, 53.5, 46.8, 29.3, 29.1, 25.7, 18.0, 7.0, 6.5, –4.7, –4.8; MS (CI) 547 (1), 518 (88), 490 (5), 341 (21), 237 (20), 209 (52), 161 (40), 121 (100), 73 (22); HRMS (EI) *m/z* $[M]^+$ calcd for $C_{29}H_{49}NO_5Si_2$ 547.3149, found 547.3152; Anal. calcd for $C_{29}H_{49}NO_5Si_2$ C 63.57, H 9.01, N 2.56, found C 63.73, H 9.11, N 2.77.

To a –78 °C slurry of the TES silyl ether of **9** (4.48 g, 8.17 mmol) in allyl alcohol (82 mL) was added *n*-BuLi (32.7 mL of a 2.5 M solution in hexanes, 81.7 mmol) dropwise over 45 min. The reaction was warmed to rt over 30 min, becoming a clear, colorless solution, and stirred at rt for 2 h, becoming cloudy yellow. The reaction was diluted with Et_2O (320 mL) and H_2O (160 mL) and stirred vigorously until all of the solids dissolved. The layers were separated, and the aqueous layer was extracted with Et_2O (160 mL). The combined organic layers were washed with saturated aqueous NaCl (160 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*, removing remaining traces of allyl alcohol under high vacuum. The crude material was purified by flash chromatography [hexanes/EtOAc (9:1)] to provide ester **57** (4.06 g, 82%) as a colorless, viscous oil. R_f 0.53 [hexanes/EtOAc (3:1)]; $[\alpha]^{22}_{D}$ –24.2 (*c* 1.71, $CHCl_3$); IR (film) 3277 (br), 3090, 3031, 2958, 1733, 1650, 1620, 1586, 1507, 1252, 1089, 1040, 873, 839, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (A of AB, J_{AB} = 8.7 Hz, 2H), 6.86 (B of AB, J_{BA} = 8.7 Hz, 2H), 5.87 (ddt, J = 17.2, 10.5, 5.8 Hz, 1H), 5.70 (A of ABXY, J_{AB} = 10.2 Hz, J_{AX} = 1.2 Hz, J_{AY} = 1.2 Hz, 1H), 5.66 (B of ABXY, J_{BA} = 10.2 Hz, J_{BX} = 2.0 Hz, J_{BY} = 0.7 Hz, 1H), 5.61 (s, br, 1H), 5.31 (ddt, J = 17.2, 1.5, 1.5 Hz, 1H), 5.20 (ddt, J = 10.5, 1.3, 1.3 Hz, 1H), 4.59 (A of AB, J_{AB} = 11.2 Hz, 1H), 4.57 (B of AB, J_{BA} = 11.2 Hz, 1H), 4.52 (ddd, J = 5.8, 1.5, 1.3 Hz, 2H), 4.05 (dddd, J = 8.3, 5.1, 1.8, 1.8 Hz, 1H), 3.80 (s, 3H), 3.36-3.24 (m, 2H), 2.97 (dd, J = 9.6, 4.1 Hz, 1H), 1.96–1.85 (m, 1H), 1.85–1.65 (m, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.87 (s, 9H), 0.52-0.67 (m, 6H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 159.2, 135.1, 132.2, 131.1, 130.0, 129.9, 118.1, 113.6, 75.7, 72.2, 66.8, 65.1, 55.4, 55.2, 49.5, 30.3, 28.7, 25.7, 18.0, 7.1, 6.6, –4.6, –4.8; MS (CI) 576 (3), 473 (21), 411 (15), 341 (17), 308 (25), 209 (25), 166 (40), 121 (100), 75 (13); HRMS (EI) *m/z* $[M - C_2H_5]^+$ calcd for $C_{30}H_{50}NO_6Si_2$ 576.3177, found 576.3196; Anal. calcd for $C_{32}H_{55}NO_6Si_2$ C 63.43, H 9.15, N 2.31, found C 63.52, H 9.12, N 2.36.

***tert*-Butyl-((2*R*,3*S*)-3-((2*R*,3*S*,4*S*)-3-(benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)tetrahydrofuran-2-yl)-3-hydroxy-2-((((4-methoxybenzyl)oxy)amino)methyl)propanoyl)-L-alaninate (58).** A flask is charged with β-lactam **29** (23 mg, 0.035 mmol) in dichloromethane (0.35 mL) and L-alanine *tert*-butyl ester hydrochloride (6.2 mg, 0.035 mmol) is added. The solution is cooled to 0 °C and 0.05 mL of trimethylaluminum (2.0 M in hexanes) is added. The mixture is allowed to warm to room temperature with stirring for an hour, after which it is filtered through a pipette column of silica gel. The solvent is then evaporated and the residue is subjected to flash silica chromatography (pentanes/diethyl ether, 1:3 by volume) leading to the desired amide **58** (18 mg) as a clear oil (56%) yield, which is characterized as follows: R_f

0.55 [pentanes/diethyl ether (1:3) 2 elutions]; IR (film) 3345, 2927, 2862, 1735, 1648, 1456, 1248, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.47–7.35 (m, 6H), 7.25–7.21 (m, 4H), 7.13–7.08 (m, 2H), 6.96 (d, *J* = 7.1 Hz, 1H), 6.86–6.80 (m, 2H), 4.65–4.57 (m, 2H), 4.43 (p, *J* = 7.1 Hz, 1H), 4.30 (d, *J* = 4.1 Hz, 1H), 4.17 (d, *J* = 11.8 Hz, 1H), 4.11 (s, 2H), 4.07 (s, 1H), 4.04–3.94 (m, 2H), 3.89 (s, 1H), 3.77 (s, 4H), 3.33 (dd, *J* = 6.3, 2.8 Hz, 2H), 2.99 (t, *J* = 6.3 Hz, 1H), 1.46 (s, 9H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 171.7, 159.4, 138.2, 135.9, 135.8, 133.4, 133.3, 130.1, 130.0, 129.9, 129.8, 128.2, 127.9, 127.8, 127.5, 127.4, 113.8, 84.3, 81.7, 81.5, 76.4, 75.7 74.5, 71.9, 69.4, 55.2, 52.7, 48.7, 45.4, 28.0, 26.9, 19.0, 18.3; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{46}H_{61}N_2O_9Si$ 813.4146, found 813.4150. We suspect that this reaction is much higher yielding than recorded above. However, the aminoalcohol **58** shows instability at room temperature when it is concentrated to a neat oil. The compound may decompose via retro-aldol or retro-Mannich processes.

Allyl (*S*)-2-[(1*R*,4*S*)-4-(*tert*-butyldimethylsilanoxy)-1-(triethylsilanoxy)cyclohex-2-enyl]-3-{[3-((1*S*,2*S*,4a*R*,6*S*,8a*S*)-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-oxopropionyl]-(4-methoxybenzyloxy)amino}propionate (60). To a rt solution of amine **57** (1.98 g, 3.27 mmol) in MeCN (26.2 mL) was added crude ketoacid **59** (901 mg, 3.60 mmol), followed by BOP (1.74 g, 3.93 mmol) and Et_3N (958 µL, 6.87 mmol). The clear, colorless solution was stirred at rt for 20 min, becoming pale yellow. Additional amounts of ketoacid **59** (450 mg, 1.8 mmol), BOP (869 mg, 1.96 mmol), and Et_3N (479 µL, 3.44 mmol) were added. The reaction was stirred at rt for 15 min, during which time a white solid precipitated and a bright yellow color developed. The reaction was diluted with Et_2O

(140 mL) and washed with H_2O (40 mL) and saturated aqueous NH_4Cl (40 mL). The combined aqueous layers were extracted with Et_2O (80 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous NaCl (40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a yellow oil. The crude material was purified by flash chromatography [hexanes/EtOAc (9:1)] to provide amide **60** (2.56 g, 93%) as a yellow oil (2.5:1 ratio of keto-enol tautomers): R_f 0.55 [hexanes/EtOAc (3:1)]; $[\alpha]_D^{22}$ –13.7 (*c* 1.35, $CHCl_3$); IR (film) 3086, 3016, 2946, 1720, 1671, 1607, 1579, 1516, 1252, 1091, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 6.91–6.85 (m, 2H), 5.77 (ddt, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.77–5.66 (m, 2H), 5.59–5.47 (m, 1H), 5.36 (t, *J* = 9.7 Hz, 1H), 5.29 (s, 0.3H), 5.22 (ddt, *J* = 17.2, 1.5, 1.5 Hz, 0.7H), 5.12 (ddt, *J* = 17.2, 1.5, 1.5 Hz, 0.3H), 5.13 (d, *J* = 10.3 Hz, 1H), 4.76 (A of AB, J_{AB} = 9.7 Hz, 0.7H), 4.70 (A of AB, J_{AB} = 10.0 Hz, 0.3 H), 4.62 (B of AB, J_{BA} = 10.0 Hz, 0.3H), 4.55 (B of AB, J_{BA} = 9.7 Hz, 0.7H), 4.50 (A of $ABXY_2$, J_{AB} = 13.1 Hz, J_{AX} = 5.9, J_{AY} = 1.5 Hz, 0.7H), 4.46 (B of $ABXY_2$, J_{BA} = 13.2 Hz, J_{BX} = 5.9, J_{BY} = 1.5 Hz, 0.7H), 4.37 (A of ABX_2, J_{AB} = 13.2 Hz, J_{AX} = 1.5 Hz, 0.3H), 4.36 (B of ABX_2, J_{AB} = 13.2 Hz, J_{AX} = 1.5 Hz, 0.3H), 4.49–4.28 (m, 1.3H), 4.21 (br d, *J* = 14.2 Hz, 0.3H), 4.11–4.03 (m, 1H), 4.01–3.86 (m, 1H), 3.80 (s, 3H), 3.79–3.75 (m, 0.3H), 3.49 (A of AB, J_{AB} = 15.0 Hz, 0.7H), 3.27 (B of AB, J_{BA} = 15.0 Hz, 0.7H), 2.89–2.82 (m, 1H), 2.72 (dd, *J* = 11.0, 5.5 Hz, 0.7H), 2.52–2.42 (m, 0.7H), 2.36–2.26 (m, 0.3H), 2.21 (dd, *J* = 11.4, 5.9 Hz, 0.3H), 2.30–1.86 (m, 2H), 1.85–1.52 (m, 5H), 1.52–1.28 (m, 3H), 0.98–0.68 (m, 18H), 0.87 (s, 9H), 0.66–0.57 (m, 6H), 0.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5, 180.3, 173.0, 172.3, 172.2, 168.5, 160.2, 160.0, 135.7, 135.5, 132.2, 132.1, 131.7, 131.5, 131.2, 131.1, 130.6, 130.6, 130.4, 130.3, 126.4, 126.0, 118.1, 113.8, 88.5, 75.6,

75.4, 72.3, 72.2, 66.7, 66.6, 65.3, 55.6, 55.5, 55.2, 50.2, 48.9, 42.5, 41.7, 41.5, 35.9, 35.7, 35.3, 35.2, 33.0, 33.0, 31.5, 30.4, 29.8, 28.9, 28.6, 25.7, 22.5, 18.0, 17.8, 17.4, 7.1, 6.6, –4.7, –4.8; MS (FAB) 860 (100); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{47}H_{75}NO_8Si_2Na$ 860.4929, found 860.4948.

(*S*)-2-[(1*R*,4*S*)-4-(*tert*-Butyldimethylsilanoxy)-1-(triethylsilanoxy)cyclohex-2-enyl]-3-{[3-((1*S*,2*S*,4a*R*,6*S*,8a*S*)-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-oxopropionyl]-(4-methoxybenzyloxy)amino}propionic acid (61). To a rt solution of ester **60** (584 mg, 0.7 mmol) in CH_2Cl_2 (6.9 mL) was added pyrrolidine (128 μL, 1.53 mmol), followed by $Pd(PPh_3)_4$ (80.5 mg, 0.0696 mmol). The bright yellow solution was stirred at rt for 10 min. The reaction was diluted with pentane (25 mL) and washed with 1:1 H_2O–saturated aqueous NH_4Cl (25 mL) then saturated aqueous NH_4Cl (25 mL). The combined aqueous layers were extracted with CH_2Cl_2 (25 mL). Then the combined organic layers were washed with saturated aqueous NaCl (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a pale yellow oil. The crude material decomposes upon standing for several hours at rt, and it decomposes rather quickly on silica gel, so flash chromatography was performed as rapidly as possible with a short, wide column at a fast elution rate, (3:1 to 2:1 hexanes/EtOAc step gradient) to provide acid **61** (424 mg, 76%) as a yellow foam of a 4:1 ratio of keto–enol tautomers contaminated with traces of PPh_3 impurities. This yield was slightly improved on smaller scale (276 mg of **60** provided 235 mg of **61** (89%). R_f 0.20 [hexanes/EtOAc (3:1)], R_f 0.42 [hexanes/EtOAc (2:1)]; $[\alpha]_D^{22}$ –30 (*c* 0.78, $CHCl_3$); IR (film) 3474–2432 (br), 3066, 3017, 2953, 1719, 1660, 1615, 1591, 1517, 1252, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2H), 6.91–6.85 (m, 2H), 5.75 (d, *J* = 10.0 Hz, 1H), 5.73 (d, *J* =

10.0 Hz, 1H), 5.53 (ddd, *J* = 9.9, 4.3, 2.7 Hz, 0.2H), 5.50 (ddd, *J* = 9.8, 4.4, 2.6 Hz, 0.8H), 5.37 (d, *J* = 9.9 Hz, 0.2H), 5.35 (d, *J* = 9.8 Hz, 0.8H), 5.28 (s, 0.2H), 4.79 (A of AB, J_{AB} = 10.3 Hz, 0.8H), 4.72 (A of AB, J_{AB} = 10.5 Hz, 0.2H), 4.65 (B of BA, J_{BA} = 10.3 Hz, 0.8H), 4.66 (B of AB, J_{BA} = 10.5 Hz, 0.2H), 4.19–4.10 (m, 1H), 4.10–4.05 (m, 1H), 3.96–3.84 (m, 1H), 3.80 (s, 2.4H), 3.79 (s, 0.6H), 3.48 (A of AB, J_{AB} = 15.2 Hz, 0.8H), 3.31 (B of AB, J_{BA} = 15.2 Hz, 0.8H), 2.96–2.88 (m, 1H), 2.73 (dd, *J* = 10.3, 5.3 Hz, 0.8H), 2.52–2.42 (m, 0.8H), 2.34–2.23 (m, 0.2H), 2.19 (dd, *J* = 11.5, 6.0 Hz, 0.2H), 2.00–1.84 (m, 2H), 1.84–1.54 (m, 6H), 1.50–1.28 (m, 2H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.94–0.70 (m, 9H), 0.87 (s, 9H), 0.65 (q, *J* = 7.8 Hz, 6H), 0.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.2, 180.8, 180.6, 174.7, 174.3, 173.4, 169.2, 160.2, 160.1, 135.0, 134.7, 131.7, 131.4, 131.3, 131.1, 130.7, 130.6, 130.2, 123.0, 126.5, 126.2, 114.0, 114.0, 88.6, 76.0, 73.5, 73.3, 65.2, 65.0, 55.8, 55.2, 55.2, 53.9, 50.8, 50.2, 48.6, 43.7, 43.6, 42.5, 41.7, 41.5, 35.9, 35.7, 35.3, 35.2, 33.1, 33.0, 31.5, 30.7, 29.8, 29.7, 29.0, 28.9, 25.7, 23.7, 22.7, 22.5, 17.9, 17.8, 17.4, 7.0, 6.5, 1.0, –4.7, –4.8; MS (FAB) 780 (37), 773 (22), 769 (69), 768 (100), 761 (20); HRMS (EI) *m/z* $[M - C_2H_5]^+$ calcd for $C_{42}H_{66}NO_8Si_2$ 768.4327, found 768.4332.

(*S*)-5-[(1*R*,4*S*)-4-(*tert*-Butyldimethylsilanoxy)-1-(triethylsilanoxy)cyclohex-2-enyl]-3-[(1*S*,2*S*,4a*R*,6*S*,8a*S*)-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl]-1-(4-methoxybenzyloxy)piperidine-2,4-dione. To a –20 °C solution of acid **61** (424 mg, 0.531 mmol) in CH_2Cl_2 (5.3 mL) was added BOP (282 mg, 0.69 mmol). The reaction was stirred for 5 min then titrated with DBU until TLC indicated the complete consumption of both the starting acid **61** and the intermediate HOBT ester (~2.3 mL of a 1.0 M solution in CH_2Cl_2, ~2.28 mmol). The reaction turned bright yellow upon addition of DBU. The mixture was diluted with pentane (10 mL) and washed with 1:1 H_2O–saturated aqueous NH_4Cl (2 x 10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a yellow oil. The crude material was purified by flash chromatography (9:1 hexanes/EtOAc) to provide the corresponding dihydropyridone of **62** (165 mg, 40%) as a white foam which was characterized as a 2:2:1:1 ratio of keto–enol tautomers and C5 epimers. R_f 0.60 [hexanes/EtOAc (3:1)], R_f 0.30 [hexanes/EtOAc (9:1)]; $[\alpha]^{22}_{D}$ +36 (*c* 0.84, $CHCl_3$); IR (film) 3012, 2953, 1685, 1670, 1651, 1613, 1551, 1512, 1252, 1099, 1035, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.34 (m, 2H), 6.94–6.86 (m, 2H), 5.85–5.58 (m, 2H), 5.58–5.47 (m, 1H), 5.42–5.33 (m, 1H), 5.04–4.89 (m, 2H), 4.32–3.36 (m, 4H), 3.82 (s, 1.75H), 3.81 (s, 1.25H), 2.91–2.82 (m, 0.25H), 2.80–2.72 (m, 0.25H), 2.72–2.66 (m, 0.5H), 2.63–2.59 (m, 0.25H), 2.55–2.51 (m, 0.25H), 2.48–2.40 (m, 0.5H), 1.96–1.38 (m, 10H), 1.10–0.68 (m, 27H), 0.66–0.52 (m, 6H), 0.90–0.59 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8, 203.1, 197.2, 195.6, 195.2, 194.9, 191.0, 190.1, 171.4, 170.3, 164.4, 163.2, 160.2, 159.9, 134.6, 134.1, 132.8, 132.3, 132.3, 132.0, 131.8, 131.7, 131.6, 131.4, 131.3, 131.2, 131.1, 131.0, 130.7, 130.6, 130.4, 130.3, 128.0, 127.9, 127.1, 126.9, 114.0, 113.8, 108.0, 107.6, 104.2, 103.4, 76.5, 76.4, 74.1, 73.8, 73.6, 73.0, 66.7, 65.8, 64.8, 64.4, 57.1, 57.1, 55.3, 55.2, 53.2, 52.8, 49.7, 49.5, 48.3, 47.7, 47.4, 46.7, 45.9, 42.0, 41.8, 41.7, 41.7, 36.3, 36.2, 36.0, 35.4, 35.3, 35.2, 33.1, 32.9, 32.7, 32.5, 31.9, 31.2, 31.0, 30.4, 30.4, 30.1, 30.0, 29.9, 29.7, 29.3, 29.2, 28.9, 28.8, 25.7, 22.5, 18.1, 18.0, 18.0, 17.8, 17.8, 7.1, 7.1, 7.1, 6.7, 6.6, 6.5, 6.5, –4.7, –4.8, –4.8; MS (FAB) 802 (100), 801 (44); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{44}H_{69}NO_7Si_2Na$ 802.4510, found 802.4518.

5-[(1*R*,4*S*)-4-(*tert*-Butyldimethylsilanoxy)-1-(triethylsilanoxy)cyclohex-2-enyl]-3-[(1*S*,2*S*,4a*R*,6*S*,8a*S*)-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl]-4-hydroxy-1-(4-methoxybenzyloxy)-1*H*-pyridin-2-one (62). To a rt solution of the dihydropyridone described above (58.9 mg, 0.076 mmol) in CH_2Cl_2 (0.76 mL) was added $BrCCl_3$ (81.9 μL, 0.83 mmol), followed by TMG (94.7 μL, 0.76 mmol) dropwise. The reaction was protected from light and stirred at rt for 10 h, becoming dark orange in color. The reaction was diluted with pentane (6 mL) and washed with 1:1 H_2O–saturated aqueous NH_4Cl (6 mL) then saturated aqueous NH_4Cl (6 mL). The combined aqueous layers were extracted with CH_2Cl_2 (6 mL). The combined organic layers were washed with saturated aqueous NaCl (6 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash silica gel chromatography (19:1 to 12:1 hexanes/EtOAc step gradient) to provide pyridone **62** (42.1 mg, 72%) as a white foam. R_f 0.33 [hexanes/EtOAc (12:1)], R_f 0.12 [hexanes/EtOAc (20:1)]; $[\alpha]_D^{22}$ +11 (*c* 0.32, CH_2Cl_2); IR (film) 3110, 3017, 2953, 1738, 1660, 1596, 1517, 1252, 1094, 1035, 839, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.30 (A of AB, J_{AB} = 8.5 Hz, 2H), 6.89 (B of AB, J_{BA} = 8.5 Hz, 2H), 5.75 (d, *J* = 10.0 Hz, 1H), 5.60 (ddd, *J* = 10.0, 4.4, 2.7 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.40 (d, *J* = 10.0 Hz, 1H), 5.15 (A of AB, J_{AB} = 11.0 Hz, 1H), 5.14 (B of AB, J_{BA} = 11.0 Hz, 1H), 4.41 (dd, *J* = 11.3, 5.7 Hz, 1H), 4.24–4.18 (m, 1H), 3.81 (s, 3H), 2.94–2.86 (m, 1H), 2.15 (ddd, *J* = 13.3, 13.3, 3.3 Hz, 1H), 1.92–1.84 (m, 2H), 1.84–1.65 (m, 4H), 1.65–1.44 (m, 3H), 1.05 (dddd, *J* = 12.6, 12.6, 12.6, 3.5 Hz, 1H), 1.00–0.76 (m, 8H), 0.91 (t, *J* = 7.8 Hz, 9H), 0.90 (s, 9H), 0.67–0.52 (m, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.7, 174.6, 160.5, 158.1, 140.3, 135.3, 131.7, 131.5, 130.6, 130.4, 125.8, 117.1, 114.2, 108.1, 78.4, 76.1, 71.2, 66.9, 55.3, 53.0, 41.8, 41.7, 36.3, 35.4, 34.7, 33.1, 31.1, 29.9, 29.7, 29.2, 25.8, 22.6, 18.1, 18.0, 7.2, 6.8, –4.6, –4.7; MS (FAB) 748 (100); HRMS (EI) *m/z* $[M – C_2H_5]^+$ calcd for $C_{42}H_{62}NO_7Si_2$ 748.4065, found 748.4088.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Proton and carbon NMR spectra of the aldol adducts of Table 3 (compounds **21**, **23**, **25**, **27**, **29**, **31**, **33**, **33a**, **35**, **35a**, **37**, **37a**, **39**, **39a**, **41**, **43**, **45** and **47**)

Proton and carbon NMR spectra of **1**, **48**, **55**, **56**, **58** and proton spectra of **8**, **9**, the TES ether of **9**, **57**, **59**, **60**, **61**, and **62**

Mosher ester analyses for the products **33** and **35** of Table 3

Crystallographic data for compound **9**

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Notes

The authors declare no competing financial interest.

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(13) In small scale reactions of **1** with ketone **7**, the use of KHMDS (2.1 equiv) for enolate formation at –78 °C produced adducts **8** and **9** in excellent yield (dr 1.6:1).

However, this procedure gave inconsistent results with an increase in reaction scale that failed to consume the starting ketone.

(14) a) To obtain suitable crystals for X-ray analysis, alcohol **9** was treated with TBSOTf and 2,6-lutidine in CH_2Cl_2 to give bis-*tert*-butyldimethylsilyl ether, which afforded colorless needles (mp 117–118 °C) $C_{29}H_{49}NO_5Si_2$, space group P2 (1). A total of 11625 reflections were measured and final residuals were R(F) = 0.1090 and R_w (F2) = 0.2670. A full report is contained in the Supporting Information. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, via www.ccdc.cam.ac.uk/data_request/cif. b) Diastereomers **8** and **9** have been individually transformed into their corresponding epoxyalcohols, and the later derivatives have been unambiguously described by X-ray crystallographic analysis (see reference 6a for details).

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