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Approach to Monobactams and Nocardicins via Diastereoselective Kinugasa Reaction

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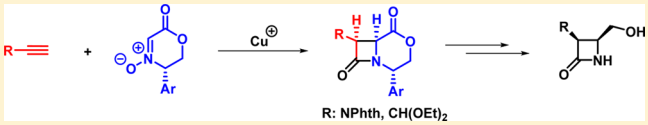
Supporting Information

ABSTRACT: A Kinugasa reaction between copper(I) acetylides and cyclic nitrones derived from chiral amino alcohols and glyoxylic acid is reported. The stereochemical preferences observed in this reaction are discussed. The alkyne molecule approaches the nitrone exclusively *anti* to the large substituent next to the nitrogen atom to provide the *cis*-substituted *β*-lactam ring preferentially. The six-membered oxazinone ring can be opened by reduction with lithium borohydride. Deprotection of the *β*-lactam nitrogen atom can be achieved by lithium in liquid ammonia reduction or by CAN oxidation, depending on the substituents attached to the four-membered azetidinone ring. The adducts obtained by the Kinugasa reaction provide an attractive entry to a variety of monocyclic *β*-lactam structures related to monobactams and nocardicins.



INTRODUCTION

The copper(I)-catalyzed reaction between terminal alkynes and nitrones in the presence of an organic base leading to *β*-lactams, known as the Kinugasa reaction,[1,2] represents an attractive approach to a variety of mono- and bicyclic *β*-lactams.[3,4]

The mechanism of the Kinugasa reaction cascade has been studied in detail.[5,6] The initial step involves 1,3-dipolar cycloaddition of a copper acetylide with the nitrone to provide the metalated isoxazoline intermediate which undergoes rearrangement to form the *β*-lactam ring. Very recently, the mechanism of the catalytic Kinugasa reaction has been investigated by means of DFT calculations.[6] The regiochemistry of the Kinugasa reaction is opposite to known moisture-sensitive additions of terminal acetylides to nitrones[7] or NHC−copper(I) halide catalyzed reactions of terminal alkynes on water, both leading to propargylic *N*-hydroxylamines.[8]

We have reported a general and highly stereoselective access to carbapenam scaffolds using nonracemic, five-membered, cyclic nitrones derived from malic and tartaric acids as well as from pentofuranosides with chiral and achiral alkynes (Scheme 1a).[2,9] It has been shown that the configuration of the bridgehead carbon atom is controlled by the configuration of the nitrone substituent located next to the carbon atom of the double bond, providing the 5,6-*cis*-substituted carbapenam as the major product.[2,9] The 5,6-*cis*/*trans* ratio depended on the structure and configuration of the alkyne, as well as the base used.[9a] In particular, we have shown that the reaction between alkyne **1** derived from D-lactic acid and 2-deoxyribose-derived nitrone **2** provided adducts, which represents an attractive entry to thienamycin **3** (Scheme 1b).[10] The reaction between **1** and **2** demonstrated that the stereogenic center next to the nitrogen atom of the cyclic nitrone controls the direction of asymmetric induction of the Kinugasa cascade similarly to the stereogenic center next to the carbon atom of the C−N double bond.[9−11]

Recently, we have described a novel approach to a key intermediate **4** for penem and carbapenem synthesis, which was based on Kinugasa reaction of *O*-silyl-protected (*R*)-3-butyn-2-ol **1** with nitrone **5** derived from *N*-benzyl hydroxylamine and benzyl glyoxylate (Scheme 1c).[12] The reaction proceeded in good yield and with high stereoselectivity at C-3 of the azetidinone ring to provide adduct **6**. The relatively high content of the *trans* isomer (25%) has been ascribed to the base-catalyzed epimerization at the C-4 carbon atom of the initially formed *cis* compound (Scheme 1c). The crude product of the Kinugasa reaction can be easily transformed into **4**. The high reactivity of nitrone **5** prompted us to employ six-membered cyclic, chiral nitrones incorporating amino alcohol and glyoxylate fragments in the Kinugasa reaction. It should be stressed that piperidine-related, chiral, six-membered nitrones displayed a similar direction of asymmetric induction in the Kinugasa reactions as their five-membered congeners but afforded lower yields which is a consequence of the lower stability of these dipoles.[13]

The synthesis of 5,6-dihydro-5-phenyl-2*H*-1,4-oxazin-2-one *N*-oxide (**7**) and related compounds, as well as their applications in 1,3-dipolar cycloadditions have been recently studied to show great potential of the adducts in the synthesis of a variety of interesting bioactive compounds.[14−18]

RESULTS AND DISCUSSION

For the present study we selected relatively stable cyclic nitrones **7**−**10** readily available from glyoxylic acid or bromoacetates and chiral amino alcohols, according to known procedures.[14−16] In the synthesis of nitrone **8**, hydroxylamino alcohol **11** was the primary intermediate, whereas in the syntheses of **9** and **10**, 5-substituted morpholin-2-ones **12** and **13**, respectively, were employed.[14−16]

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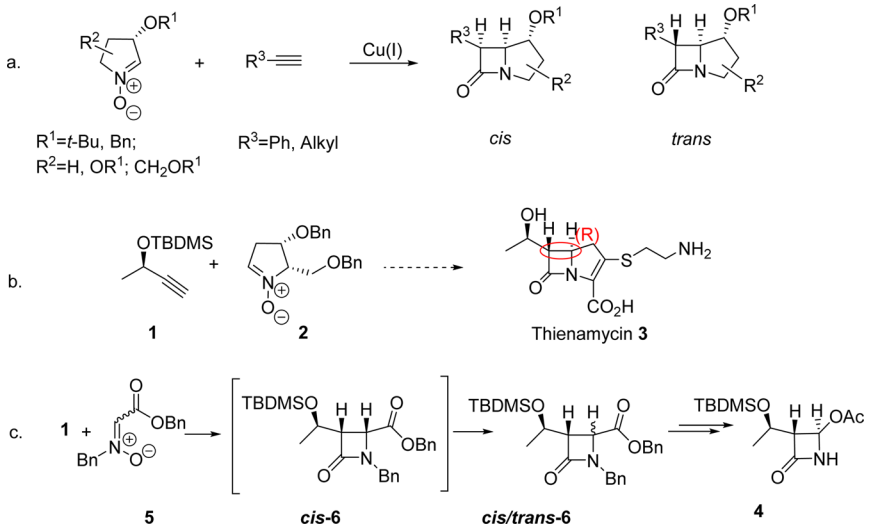
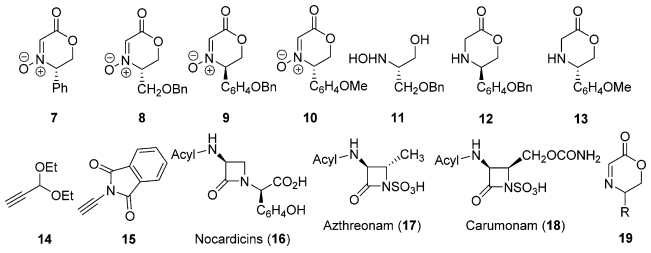
Scheme 1



As the acetylene partner, commercially available compound **14** was chosen in order to compare the stereochemical pathway of the investigated reactions with those performed previously on nitrones related to pyrrolidine[2,9,11a] and pyrimidine.[13] We also selected the readily available and relatively stable compound **15**,[17] which allowed us to attach an amino function to the carbon atom next to the *β*-lactam carbonyl group. Making the choice of acetylene **15** we expected some difficulties due to the known sensitivity of phthalimides to basic reagents.[18,19]

We anticipated the products of the Kinugasa reaction to form a multifunctional scaffold consisting of a six-membered oxazine ring fused to the four-membered *β*-lactam ring (O-2-isocephams). The opening of the six-membered ring and deprotection of the *β*-lactam nitrogen atom were expected to provide an entry to a variety of monocyclic *β*-lactams. Particularly interesting are alkyne **15** and nitrones **7**−**10** since their combination should provide an entry to nocardicins **16** and monobactams such as aztreonam **17**[20] and carumonam **18**.[21]



Because of the high reactivity of nitrones **7**−**10**, their reactions with alkynes **14** and **15**, after optimization, were performed in acetonitrile at −30 °C or −35 °C with Et_3N and 2 equiv of CuCl. At higher temperatures, under the reaction conditions, nitrones **7**−**10** underwent fast *N*-deoxygenation to the corresponding imines **19** which, in the case of **7**, **9**, and **10** (R = Ar), were prone to a double bond shift to form achiral compounds.[22]

All of the investigated reactions between nitrones **7**−**10** and alkynes **14** and **15** provided only one set of *cis*/*trans* adducts with preference for the formation of the *cis*-substituted azetidinone rings **20**, **22**, **24**, **26**, **28**, **30**, and **32** with ratios of isomers varying from 10:2 to 10:7 (Schemes 2 and 3).

Cis and *trans* substitution patterns were ascribed on the basis of coupling constants between the protons on the four-membered ring (H-6, H-7, J_{H-H} 5−6 Hz for *cis* product and J_{H-H} 2−3 Hz for *trans* isomer), whereas the absolute configuration at the bridgehead carbon atom was assigned by NOE experiments between protons of the morpholine fragment of the 4-oxacepham (oxa-isocepham) skeleton. In the case of adducts **24**, **29**, **30**, and **32**, the structures and configurations were confirmed by X-ray crystallography (Figure 1). It should be stressed that the 6,7-*cis*-substituted compounds **24**, **26**, **28**, and **32** displayed a higher rotation barrier of the *N*-phthaloyl group, which was evidenced in the NMR spectra at room temperature by nonequivalence of carbonyl groups and even all aromatic nuclei.

The acetylene molecule approached the nitrone exclusively *anti* with respect to the substituent in the latter. In the case of adducts derived from alkyne **14**, whereas *trans* compounds **21**, **23**, and **31** were only noticed in the corresponding postreaction mixtures; *cis* adducts **20**, **22**, and **30** were purified by crystallization. *Trans* adducts **25**, **29**, and **33** derived from alkyne **15** were separated from the *cis* congeners by chromatography. Unfortunately *trans* compound **27** was not isolated and observed only in the NMR of the crude reaction mixture. As expected, the reaction between alkyne **15** and nitrone **9**, whose configuration of the benzylic stereogenic center matched the configuration of nocardicins, provided the *cis* adduct **32** with the absolute configuration of the center next to the *β*-lactam carbonyl group, opposite to the desired. Compound **33** with the correct configuration at that center, the *trans* adduct, was obtained in 15% yield only after chromatographic separation. Due to similar acidity of both protons of the *β*-lactam ring (H-6 and H-7), a possible base-catalyzed epimerization of the Kinugasa adduct **32** would provide a mixture of diastereomers. It should be stressed, however, that after transformation of the ester group into a protected hydroxymethyl group, an epimerization next to the *β*-lactam carbonyl group should be possible.[23]

The observed direction of asymmetric induction of the investigated process can be easily explained according to our previous reports.[9] Since the Kinugasa reaction is a cascade process, its asymmetric course is governed mostly by the initial cycloaddition step. As can be seen from Figure 2A, the copper acetylide complex can approach the nitrone partner from any of its two faces. The *anti* approach of the acetylide, with respect to the substituent at the C-6 position in the nitrone, should be favored due to lack of steric interaction that can occur in the case of attack from the opposite nitrone face. This stage of the cascade

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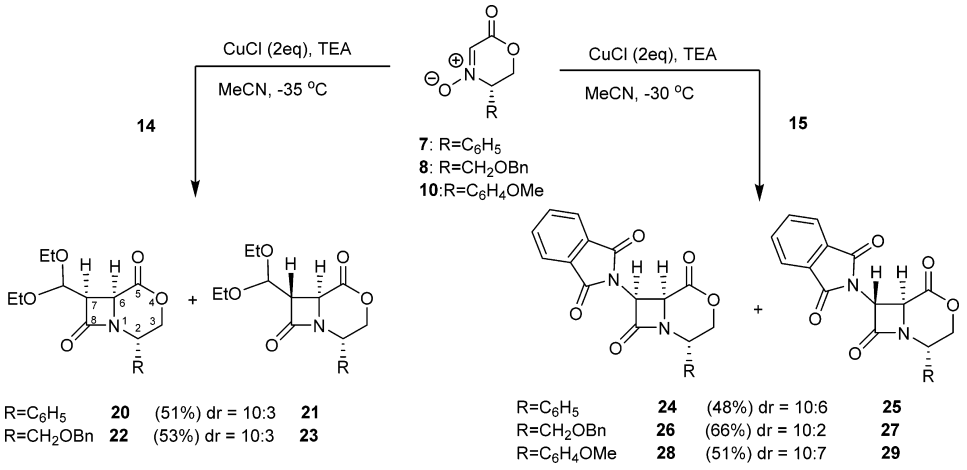
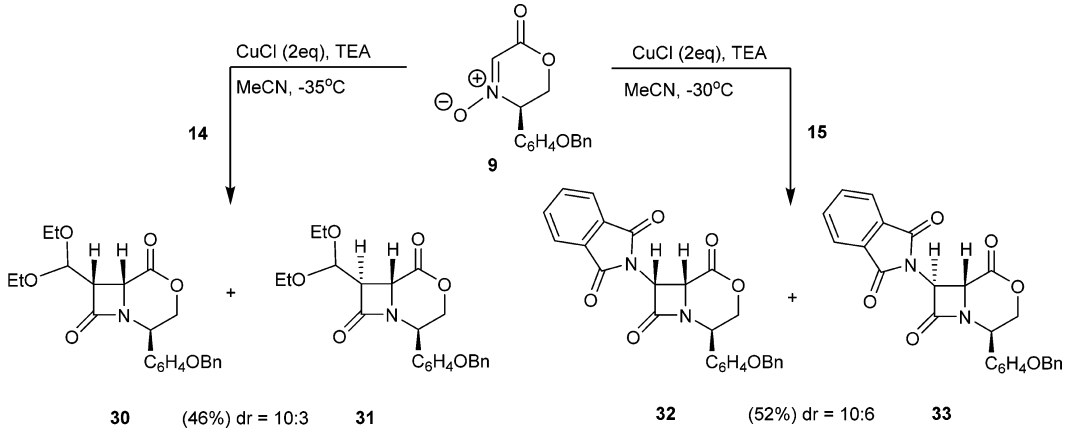
Scheme 2



Scheme 3



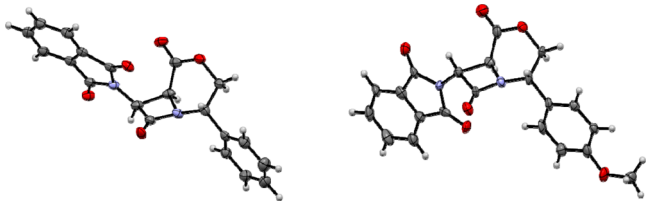


Figure 1. ORTEP plots of *cis*-**24** and *trans*-**29** with 50% probability ellipsoids.

is also the rate-determining one. It has been indicated very recently by DFT calculations by Himo and co-workers.[6] Once the cycloadduct formed rearranges to the corresponding β-lactam enolate, it subsequently undergoes protonation to provide the desired product.

The protonation may lead to *cis*- and *trans*-2-azetidinone derivatives (Figure 2B), and its course may be controlled either by kinetic or thermodynamic factors. In most cases, *cis* products are the major ones, indicating an influence of the kinetic factor

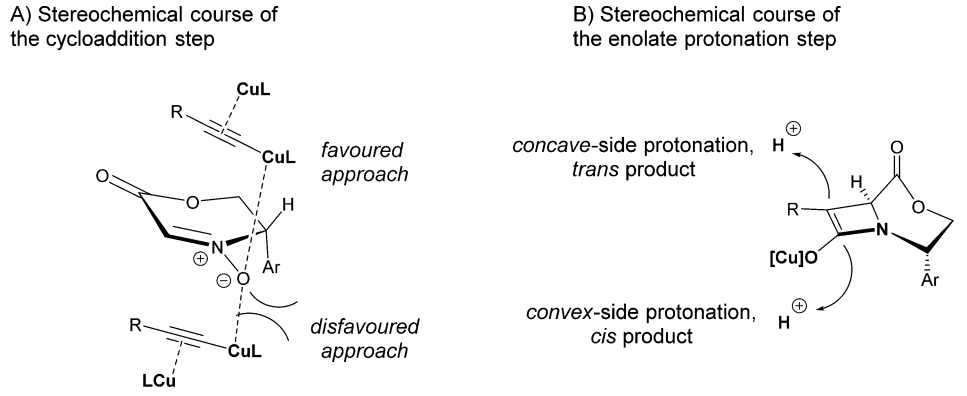


Figure 2.

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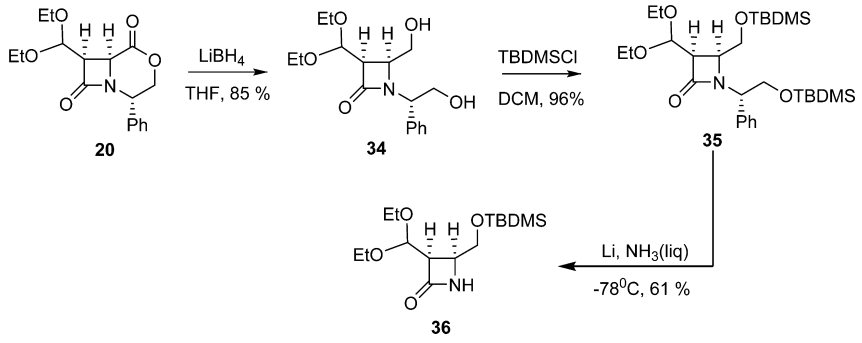
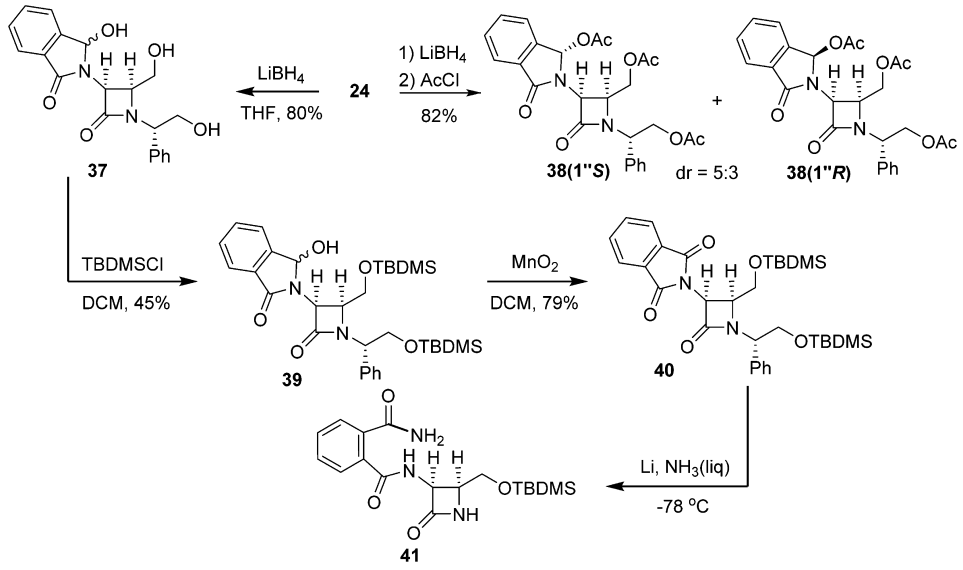
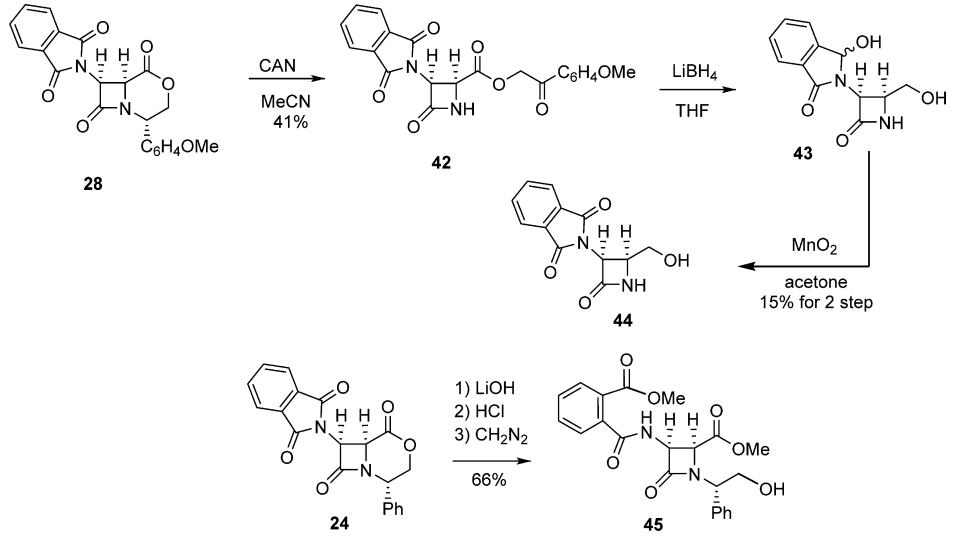
Scheme 4



Scheme 5



Scheme 6



which is the result of the more favored approach of a proton from the less shielded face of the bicyclic enolate (*syn* attack to bridgehead proton). Again, the protonation from the other side is less favorable due to steric hindrance.

For further investigations, compounds **20**, **24**, and **28** were selected. Compound **20** was reduced with $LiBH_4$ to afford the *N*,3,4-trisubstituted azetidinone **34**, which was subsequently silylated with TBDMSCl. Silyl-protected compound **35** was then subjected to reduction with lithium in liquid ammonia to give *N*-deprotected azetidinone **36** in 60% yield (Scheme 4). The performed reaction sequence demonstrated that disubstituted azetidinones with defined configuration at both stereogenic

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centers could be easily obtained by the Kinugasa reaction, while asymmetric induction depended on the stereogenic center attached to the β-lactam nitrogen atom.

Opening of the six-membered ring in adduct **24** or **28** confirmed the expected sensitivity of the *N*-phthaloyl protecting group to bases.[18] Reduction of the lactone carbonyl group in **24** with $LiBH_4$ also led to the reduction of one phthaloyl carbonyl, providing the corresponding mixture of cyclic acetals of *o*-formylbenzamide **37**. Diastereomeric acetals **37** were acetylated and characterized after chromatographic separation as (1″*S*) and (1″*R*) triacetates **38**, and the configuration of the acetal center C-1″ was proved by X-ray crystal structure analysis of the diastereomer (1″*R*). The silylation of **37** with TBDMSCl provided the corresponding disilyl derivative **39**, which was reoxidized with MnO_2 to afford the corresponding phthaloyl compound **40** (Scheme 5).

Deprotection of the β-lactam nitrogen atom in adduct **24** by catalytic hydrogenation of the C−N bond using a palladium catalyst failed. As expected, the reduction of compound **40**, which did not contain the fused oxazine ring, using lithium in liquid ammonia, provided a complicated mixture of products as a result of multiple competing reactions of the phthaloyl residue under the reaction conditions. We isolated and characterized only *N*-deprotected compound **41** and a product of partial reduction of the phthaloyl group **39**. On the other hand, oxidative cleavage of the C−N bond in compound **28** with CAN provided the ester **42**, which was subsequently reduced with $LiBH_4$ to a mixture of cyclic acetals **43** which was reoxidized with MnO_2 to afford compound **44** (Scheme 6).

The same sensitivity of phthaloyl protection to bases was demonstrated by LiOH-mediated opening of the lactone **24**, which also caused opening of the phthaloyl residue to provide a lithium salt of the diacid. Esterification of the crude diacid with diazomethane provided diester **45**, which was characterized (Scheme 6).

CONCLUSIONS

We have shown that 5-substituted tetrahydro-2*H*-1,4-oxazin-2-one *N*-oxides with a defined configuration of the stereogenic center derived from the corresponding amino acid precursors offer an attractive entry to optically pure bicyclic β-lactams via a Kinugasa reaction. This demonstrates that, as in the case of the previously investigated nitrone **2**,[9b] the stereogenic center next to the nitrogen atom of the cyclic nitrone controls the direction of asymmetric induction of the Kinugasa cascade. Nitrones **7**−**10** not only provide 4-oxacephams (O-2-isocephams) but, after opening of the six-membered ring, also afford compounds related to monobactams and nocardicins. It should be stressed, however, that an effective strategy to introduce an amino group to the C-3 carbon atom of the azetidinone ring would require employing amino acetylene protected with a group more resistant to bases than phthaloyl.

It should be pointed out that *N*-deprotected β-lactams **36**, **41**, **42**, and **44** offer an attractive entry to a variety of monobactam structures such as carumonam **18**.

EXPERIMENTAL SECTION

Compound **7** was obtained following the reported literature procedure.[16] Nitrones **8**, **9**, and **10** were prepared according to literature procedures via suitable intermediates **11** (used crude for the next step),[16] **12**,[24] and **13**,[24] respectively. Alkyne **14** is commercially available, and acetylene **15** was obtained by the standard literature method.[17]

(5*S*)-3,4,5,6-Tetrahydro-5-benzyloxymethyl-2*H*-1,4-oxazin-2-one *N*-Oxide (8). Compound **8** was obtained from (*R*)-3-benzyloxy-2-hydroxylaminopropan-1-ol (**11**) following the procedure described for **7**:[15] yield 32% in two steps; mp 53−54 °C; $[\alpha]_D$ +10 (*c* 1.61, $CHCl_3$); IR (film) ν 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 7.21 (s, 1H), 4.70−4.58 (m, 2H), 4.60, 4.53 (ABq, *J* = 11.9 Hz, 2H), 4.13 (m, 1H), 4.03 (dd, *J* = 10.0, 6.3 Hz, 1H), 3.85 (dd, *J* = 10.0, 3.5 Hz, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 158.4, 136.8, 128.6, 128.2, 127.8, 125.8, 73.9, 66.7, 65.7, 64.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{13}NO_4Na$ [M + Na^+] 258.0742, found 258.0736.

(5*R*)-5-(*p*-Benzyloxyphenyl)morpholine-2-one (12). (*R*)-2-(*p*-Benzyloxyphenyl)-2-aminoethanol (2.43 g, 10 mmol) was suspended in acetonitrile (70 mL) under argon atmosphere. Diisopropylethylamine (2 mL, 11.5 mmol) was added to the mixture with stirring, and then a solution of phenyl bromoacetate (2.37 g, 11 mmol) in 50 mL of acetonitrile was added dropwise during 1 h. The mixture was stirred at rt for 1.5 h. Subsequently, the solvent was removed under reduced pressure at rt. The residue was purified on a silica gel column using hexane/ethyl acetate 4:6 v/v as the eluent to afford **12**, 1.10 g (38% yield), as colorless crystals: mp 132−134 °C; $[\alpha]_D$ −73 (*c* 0.34, $CHCl_3$); IR (film) ν 1739 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.43−7.28 (m, 7H), 6.98−6.95 (m, 2H), 5.05 (s, 2H), 4.35 (dd, *J* = 3.7, 10.9 Hz, 1H), 4.25 (dd, *J* = 10.5, 10.9, 1H, 4.11 (dd, *J* = 3.7, 10.5 Hz, 1H), 3.92 (d, *J* = 17.8 Hz, 1H), 3.82 (d, *J* = 17.8, 1H); ^{13}C NMR (150 MHz $CDCl_3$) δ 167.6, 159.0, 136.7, 129.7, 128.6, 128.2, 128.1, 127.4, 115.2, 74.5, 70.1, 56.0, 48.6; HRMS (ESI-TOF) *m*/*z* calcd for [M + H^+] $C_{17}H_{18}NO_3$ 284.1287, found 284.1284

(5*S*)-5-(*p*-Methoxyphenyl)morpholine-2-one (13). (*S*)-2-(*p*-Methoxyphenyl)-2-aminoethanol (0.67 g, 4.0 mmol) was suspended in acetonitrile (35 mL) under argon atmosphere. To the stirred mixture was added diisopropylethylamine (0.8 mL, 4.6 mmol), and then a solution of phenyl bromoacetate (0.95 g, 4.4 mmol) in 20 mL of acetonitrile was added dropwise during 14 h. The mixture was then stirred at rt for 2 h. Subsequently, the solvent was removed in vacuo at 20 °C. The residue was purified on a silica gel column using hexane/ethyl acetate 4:6 v/v as the eluent to yield **13**, 0.33 g (39% yield), as a light yellow solid: mp 117−121 °C; $[\alpha]_D$ +21 (*c* 0.62, $CHCl_3$); IR (film) ν 1741 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$) δ 7.33−7.30 (m, 2H), 6.92- 6.88 (m, 2H), 4.36 (dd, *J* = 3.8, 10.8 Hz, 1H), 4.27 (dd, *J* = 10.4, 10.8, 1H), 4.13 (dd, *J* = 10.4, 10.8 Hz, 1H), 3.95 (d, *J* = 17.9 Hz, 1H), 3.84 (d, *J* = 17.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ 167.6, 159.8, 129.4, 128.1, 114.3, 74.5, 56.0, 55.3, 48.6; HRMS (ESI-TOF): Calcd for [M + Na^+] $C_{11}H_{13}NO_3Na$ 230.0793; Found 230.0793

(5*R*)-3,4,5,6-Tetrahydro-5-(*p*-benzyloxyphenyl)-2*H*-1,4-oxazin-2-one *N*-Oxide (9). To dichloromethane (45 mL) were added purified *m*-chloroperoxybenzoic acid (1.58 g, 9.2 mmol) and K_2HPO_4 (3.63 g, 20.8 mmol), and the mixture was stirred for 5 min. Subsequently, the mixture was cooled to 0 °C, and a solution of **12** (1.18 g, 4.2 mmol) in dichloromethane (DCM, 10 mL) was added dropwise. The mixture was stirred with cooling for 15 min, and then stirring was continued for 2.5 h at rt. A saturated solution of $Na_2S_2O_3$ in water (15 mL) was then added. and the mixture was stirred for 5 min. Subsequently, ethyl acetate (110 mL) and water (60 mL) were added. and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 × 40 mL). The combined organic solutions were washed with 10% Na_2CO_3 in water (90 mL) and brine (30 mL), dried with Na_2SO_4, and evaporated. The residue was purified on a silica gel column using hexane/ethyl acetate 3:2 v/v as the eluent to afford **9**, 0.70 g, as a light yellow solid (56% yield): mp 121−122 °C; $[\alpha]_D$ +81 (*c* 0.92, $CHCl_3$); IR (film) ν 1723 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.42−7.36 (m, 4H), 7.34−7.28 (m, 3H), 7.23 (s, 1H), 7.01−6.98 (m, 2H), 5.07 (s, 2H), 5.00 (dd, *J* = 4.2, 5.2 Hz, 1H), 4.77 (dd, *J* = 4.2, 12.5 Hz, 1H), 4.70 (dd, *J* = 5.2, 12.5 Hz, 1H); ^{13}C NMR (150 MHz $CDCl_3$) δ 160.0, 158.5, 136.4, 129.1, 128.7, 128.2, 127.4, 124.8, 123.5, 115.6, 70.8, 70.1, 67.6; HRMS (EI) *m*/*z* calcd for [M^+] $C_{17}H_{15}NO_4$ 297.1001, found 297.0995

(5*S*)-3,4,5,6-Tetrahydro-5-(*p*-methoxyphenyl)-2*H*-1,4-oxazin-2-one *N*-Oxide (10). To DCM (20 mL) were added purified *m*-chloroperoxybenzoic acid (0.49 g, 2.8 mmol) and K_2HPO_4 (1.10 g, 6.3 mmol), and the mixture was stirred for 5 min. Subsequently, the

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mixture was cooled to 0 °C, and a solution of **13** (0.27 g, 1.31 mmol) in DCM (7 mL) was added dropwise. The mixture was stirred with cooling for 15 min, and then stirring was continued for 2 h at rt. A saturated solution of $Na_2S_2O_3$ in water (10 mL) was then added, and the mixture was stirred for 5 min. Subsequently, ethyl acetate (30 mL) and water (20 mL) were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic solutions were washed with 10% Na_2CO_3 in water (30 mL) and brine (10 mL), dried with Na_2SO_4, and evaporated. The residue was purified on a silica gel column using DCM/acetone 98:2 v/v as the eluent to afford **10**, 182 mg, as a light yellow solid (62% yield): mp 111−112 °C; $[\alpha]_D$ −4 (*c* 0.52, $CHCl_3$); IR (film) ν 1722 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.24 (s, 1H), 6.95−6.91 (m, 2H), 5.02 (dd, *J* = 4.1, 5.0 Hz, 1H), 4.80 (dd, *J* = 4.1 12.5 Hz, 1H), 4.72 (dd, *J* = 5.0 12.5 Hz) 3.81 (s, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ 160.9, 158.6, 129.1, 124.8, 123.2, 114.7, 70.9, 67.6, 55.4; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{11}H_{11}NO_4$ 244.0586, found 244.0595.

General Procedure for Kinugasa Reaction. To a suspension of CuCl (198 mg, 2 mmol) in dry degassed MeCN (5 mL) was added triethylamine (0,56 mL, 4 mmol), and after the mixture was cooled to 0 °C, alkyne **14** or **15** (1 mmol) was added. The mixture was cooled to −35 °C for 15 min, and then a solution of the nitrone in MeCN was added dropwise. The mixture was stirred, and the temperature was maintained until TLC (hexane/ethyl acetate for reactions involving **14** and toluene/ethyl acetate for reactions involving **15**) indicated no further reaction progress. The mixture was then evaporated under reduced pressure, and the ratio of *cis* and *trans* diastereomers was assigned using the ^1H NMR spectrum of the crude postreaction mixture.

(2*S*,6*S*,7*S*)-2-Benzyloxymethyl-7-(diethoxymethyl)-4-oxacepham-5,8-dione (22). Compound **22** was obtained from nitrone **8** and acetylene **14** following the general procedure (ratio of **22**:**23** = 10:3). The product **22** was purified by crystallization (53% yield): mp 83−85 °C; $[\alpha]_D$ −19 (*c* 0.51, DCM); IR (film) ν 1766 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.18−7.12 (m, 5H), 4.85 (d, *J* = 1.9 Hz, 1H), 4.61 (dd, *J* = 4.4, 11.4 Hz, 1H), 4.55, 4.51 (ABq, J = 12.1 Hz, 2H), 4.39 (dd, *J* = 3.0, 11.4 Hz, 1H), 4.12 (d, *J* = 5.8 Hz, 1H), 4.06−4.02 (m, 1H), 3.78 (dd, *J* = 1.9, 5.8 Hz, 1H), 3.77−3.64 (m, 3H), 3.64−3.61 (m, 2H), 3.41−3.35 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz $CDCl_3$) δ 168.1, 167.1, 137.3, 128.5, 128.0, 127.6, 98.7, 73.6, 69.3, 68.2, 64.2, 63.1, 59.1, 48.3, 46.8, 15.4, 14.3; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{19}H_{25}NO_6Na$ 386.1580, found 386.1576. Diastereoisomer **23** was not isolated and characterized.

(2*S*,6*S*,7*S*)-2-Phenyl-7-(diethoxymethyl)-4-oxacepham-5,8-dione (20). Compound **20** was obtained from nitrone **7** and acetylene **14** following the general procedure. The product was purified by crystallization (DCM/Et_2O), 51% yield (ratio of **20**:**21** = 10:3): mp 89−91 °C; $[\alpha]_D$ −16 (*c* 0.42, DCM); IR (film) ν 1761 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.40−7.31 (m, 5H), 5.04 (dd, *J* = 4.5, 5.0 Hz, 1H), 4.94 (d, *J* = 1.9 Hz, 1H), 4.78 (dd, *J* = 4.5, 11.7 Hz, 1H), 4.55 (dd, *J* = 5.0, 11.7 Hz, 1H), 4.19 (d, *J* = 5.8 Hz, 1H), 3.86 (dd, *J* = 1.9, 5.8 Hz, 1H), 3.83−3.68 (m, 3H), 3.44−3.38 (1H, m), 1.24 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz $CDCl_3$) δ 167.8, 167.3, 134.7, 129.1, 128.5, 126.6, 98.7, 70.5, 64.2, 63.1, 58.7, 50.9, 47.8, 15.4, 14.5; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{17}H_{21}NO_5Na$ 342.1317, found 342.1323.

^1H NMR signals characteristic for **(2*S*,6*S*,7*R*)-2-phenyl-7-(diethoxymethyl)-4-oxacepham-5,8-dione (21)** found in the crude postreaction mixture: (150 MHz $CDCl_3$) δ 4.98 (dd, *J* = 5.4, 11.6 Hz, 1H), 4.94 (m, 1H), 4.56 (dd, *J* = 5.4, 12.2 Hz, 1H), 4.44 (d, *J* = 2.0 Hz, 1H), 4.17 (dd, *J* = 11.6, 12.2 Hz, 1H), 3.83- 3.79 (m, 1H).

(2*R*,6*R*,7*R*)-2-*p*-Benzyloxyphenyl-7-(diethoxymethyl)-4-oxacepham-5,8-dione (30). Compound **30** was obtained from nitrone **9** and acetylene **14** following the general procedure. The product **30** was purified by crystallization (DCM/Et_2O), 46% yield (ratio of **30**:**31** = 10:3): mp 98−100 °C; $[\alpha]_D$ −8 (*c* 1.08, DCM); IR (film) ν 1765 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.42−7.24 (m, 7H), 6.98−6.95 (m, 2H), 5.05 (s, 2H), 4.99 (dd, *J* = 4.4, 4.9 Hz, 1H), 4.93 (d, *J* = 1.7 Hz, 1H), 4.74 (dd, *J* = 4.4, 11.7 Hz, 1H), 4.52 (dd, *J* = 4.9, 11.7 Hz, 1H), 4.15 (d, *J* = 5.9 Hz, 1H), 3.83 (dd, *J* = 1.7, 5.9 Hz, 1H), 3.82−3.68 (m, 3H), 3.44−3.38 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz $CDCl_3$) δ 167.7, 167.3, 158.8, 136.3, 128.6, 128.1, 127.9, 127.4, 126.8, 115.4, 98.7, 70.5, 70.1, 64.2, 63.1, 58.6, 50.4, 47.7, 15.4, 14.5; HRMS (ESI-TOF) *m*/*z* calcd for $[M + NH_4^+]$ $C_{24}H_{31}N_2O_6$ 443.2182, found 443.2174;

^1H NMR signals characteristic for **(2*R*,6*R*,7*S*)-2-*p*-benzyloxyphenyl-7-(diethoxymethyl)-4-oxacepham-5,8-dione (31)** found in the crude postreaction mixture: (400 MHz $CDCl_3$) δ 4.53 (dd, *J* = 5.4, 12.1 Hz, 1H), 4.43 (d, *J* = 2.0 Hz, 1H), 4.19−4.13 (m, 1H)

(2*S*,6*S*,7*S*)-2-Benzyloxymethyl-7-*N*-phthalimido-4-oxa-cepham-5,8-dione (26). Compound **26** was obtained from nitrone **8** and acetylene **15** following the general procedure. The product **26** was purified by chromatography using DCM/acetone 98:2 v/v (ratio of **26**:**27** = 5:1): mp 120−121 °C; $[\alpha]_D$ +26 (*c* 1.27, DCM); IR (film) ν 1771, 1720 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.90−7.85 (m, 1H), 7.83−7.79 (m, 1H), 7.78−7.71 (m, 2H), 7.39−7.35 (m, 2H), 7.34−7.29 (m,3H), 5.74 (d, *J* = 5.7 Hz, 1H), 4.85 (dd, *J* = 5.0, 11.9 Hz, 1H), 4.58, 4.54 (ABq, J = 12.0 Hz, 2H), 4.48 (dd, *J* = 7.3 11.9 Hz, 1H), 4.36 (d, *J* = 5.7 Hz), 4.28−4.24 (m, 1H), 3.73−3.68 (m, 2H); ^{13}C NMR (150 MHz $CDCl_3$) δ 167.1, 165.6 (×2), 137.2, 134.6, 128.6, 128.1, 127.7, 124.1, 123.9, 73.7, 68.6, 68.5, 57.2, 50.1, 48.6; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{22}H_{18}N_2O_6Na$ 429.1063, found 429.1056. The diastereomer **27** was not isolated and characterized.

(2*S*,6*S*,7*S*)-2-Phenyl-7-*N*-phthalimido-4-oxacepham-5,8-dione (24) and (2*S*,6*S*,7*R*)-2-Phenyl-7-*N*-phthalimido-4-oxacepham-5,8-dione (25). Compounds **24** and **25** were obtained from nitrone **7** and acetylene **15** following the general procedure. Diastereomers **24** and **25** were separated by chromatography using DCM/acetone 98:2 v/v as the eluent to afford **24** (38%) and **25** (10%). Compound **24**: mp 232−234 °C; $[\alpha]_D$ + 90 (*c* 0.83, DCM); IR (film) ν 1755, 1716 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.90−7.89 (m, 1H), 7.84−7.83 (m, 1H), 7.78- 7.73 (m, 2H), 7.44−7.35 (m, 5H), 5.86 (d, *J* = 5.7 Hz, 1H), 5.24 (dd, *J* = 5.1, 9.7 Hz, 1H), 4.80 (dd, *J* = 5.1, 12.4 Hz, 1H), 4.54 (d, *J* = 5.7 Hz, 1H), 4.42 (dd, *J* = 9.7, 12.4 Hz, 1H); ^{13}C NMR (150 MHz $CDCl_3$) δ 168.2, 167.1, 165.8, 165.6, 134.7, 131.9, 131.2, 129.3, 128.9, 126.4, 124.1, 124.0, 70.5, 57.0, 53.6, 49.9; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{20}H_{14}N_2O_5Na$ 385.0800, found 385.0799

Compound **25**: mp 270 °C dec; $[\alpha]_D$ +51 (*c* 0.26, CH_3CN); IR (film) ν 1770, 1722 cm^{-1}; 1H NMR (500 MHz $CDCl_3$) δ 7.95−7.91 (m, 2H), 7.82−7.78 (m, 2H), 7.55−7.51 (m, 2H), 7.50−7.46 (m, 2H), 7.42−7.37 (m, 1H), 5.71 (d, *J* = 2.2 Hz, 1H), 5.12 (dd, *J* = 5.4, 11.4 Hz, 1H), 4.87 (d, *J* = 2.2 Hz, 1H), 4.65 (dd, *J* = 5.4, 12.4 Hz, 1H), 4.25 (dd, *J* = 11.4, 12.4 Hz, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ 168.3, 166.6, 164.0, 134.8, 134.1, 131.5, 129.4, 129.0, 126.0, 124.0, 70.8, 58.3, 54.6, 53.5; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{20}H_{14}N_2O_5Na$ 385.0800, found 385.0797

(2*S*,6*S*,7*S*)-2-*p*-Methoxyphenyl-7-*N*-phthalimido-4-oxacepham-5,8-dione (28) and (2*S*,6*S*,7*R*)-2-*p*-Methoxyphenyl-7-*N*-phthalimido-4-oxacepham-5,8-dione (29). Compounds **28** and **29** were obtained from nitrone **10** and alkyne **15** in a ratio of about 10:7 following the general procedure. Diastereomers were separated by chromatography using DCM/acetone 98:2 v/v as the eluent.

28: 34%; mp 262 °C dec; $[\alpha]_D$ +50 (*c* 0.18, DMF) IR (film) ν 1794, 1759, 1715 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.91−7.87 (m, 1H), 7.84−7.81 (m, 1H), 7.78−7.72 (m, 2H), 7.33−7.30 (m, 2H), 6.95−6.92 (m, 2H), 5.84 (d, *J* = 5.7 Hz, 1H), 5.19 (dd, *J* = 5.0, 9.6 Hz, 1H), 4.77 (dd, *J* = 5.0, 12.2 Hz, 1H), 4.51 (d, *J* = 5.7 Hz, 1H), 4.41 (dd, *J* = 9.6, 12.2 Hz, 1H), 3.81 (s, 1H); ^{13}C NMR (150 MHz $CDCl_3$) δ 170.8, 169.8, 168.5, 168.3, 162.7, 137.3, 134.6, 133.9, 130.4, 129.3, 126.8, 126.7, 117.3, 73.2, 59.6, 58.0, 55.8, 52.5; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{21}H_{16}N_2O_6Na$ 415.0906, found 415.0905

29: 17%; mp 262 °C dec; $[\alpha]_D$ +79 (*c* 0.36, DMSO); IR (film) ν 1760, 1718 cm^{-1}; ^1H NMR (600 MHz (benzen d_6-DMSO d_6 1:1) δ 7.91−7.87 (m, 2H), 7.80−7.78 (m, 2H), 7.64−7.61 (m, 2H), 7.07−7.03 (m, 2H), 5.84 (d, *J* = 2.3 Hz, 1H), 5.19 (d, *J* = 2.3 Hz, 1H), 5.15 (dd, *J* = 5.2, 11.2 Hz, 1H), 4.66 (dd, *J* = 5.2, 11.8 Hz, 1H), 4.50 (dd, *J* = 11.2, 11.8 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (150 MHz, benzene-d_6−DMSO-d_6 1:1) δ 169.7, 167.1, 165.1, 159.9, 135.2, 131.7, 128.6, 128.4, 128.2, 123.9, 114.7, 70.6, 57.9, 55.5, 53.9, 53.8; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{21}H_{16}N_2O_6Na$ 415.0906, found 415.0890

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(2*R*,6*R*,7*R*)-2-*p*-Benzyloxyphenyl-7-*N*-phthalimido-4-oxacepham-5,8-dione (32) and (2*R*,6*R*,7*S*)-2-*p*-Benzyloxyphenyl-7-*N*-phthalimido-4-oxacepham-5,8-dione (33). Compounds **32** and **33** were obtained from nitrone **9** and acetylene **15** in a ratio of about 10:6 following the general procedure. Diastereomers were separated by chromatography using DCM/acetone 98:2 v/v as the eluent.

32: 42%; mp 270 °C dec; $[\alpha]_D$ −69 (*c* 0.68, $CHCl_3$); IR (film) ν 1768, 1720 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.92−7.87 (m, 1H), 7.85−7.81 (m, 1H), 7.78−7.72 (m, 2H), 7.45−7.36 (m, 4H), 7.35−7.29 (m, 3H), 7.04- 6.98 (m, 2H), 5.84 (d, *J* = 5.6 Hz, 1H), 5.18 (dd, *J* = 5.0, 9.7 Hz, 1H), 5.07 (s, 2H), 4.76 (dd, *J* = 5.0, 12.1 Hz, 1H), 4.51 (d, *J* = 5.6 Hz, 1H), 4.40 (dd, *J* = 9.7, 12.1 Hz, 1H); ^{13}C NMR (150 MHz $CDCl_3$) δ 168.2, 167.1, 165.9, 165.7, 159.2, 136.6, 134.7, 131.9, 131.2, 128.6, 128.1, 127.8, 127.4, 126.9, 124.1, 124.0, 115.6, 70.6, 70.1, 57.0, 53.1, 49.8; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{27}H_{20}N_2O_6Na$ 491.1219, found 491.1222

33: 10%; mp 223−226 °C dec; $[\alpha]_D$ −60 (*c* 0.48, DCM); IR (film) ν 1761, 1715 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.94−7.90 (m, 2H), 7.81−7.77 (m, 2H), 7.45−7.37 (m, 6H), 7.35−7.31 (m, 1H), 7.08−7.03 (m, 2H), 5.68 (d, *J* = 1.9 Hz, 1H), 5.08 (s, 2H), 5.06 (dd, *J* = 5.3, 11.6 Hz, 1H), 4.84 (d, *J* = 1.9 Hz, 1H), 4.58 (dd, *J* = 5.3, 12.4 Hz, 1H), 4.21 (dd, *J* = 11.6, 12.4 Hz, 1H); ^{13}C NMR (150 MHz $CDCl_3$) δ 168.3, 166.6, 164.0, 159.3, 136.7, 134.8, 131.5, 128.6, 128.1, 127.4, 127.3, 126.2, 124.0, 115.8, 70.9, 70.1, 58.2, 54.2, 53.5; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{27}H_{20}N_2O_6Na$ 491.1219, found 491.1216.

(1′*S*,3*S*,4*S*)-*N*-(2′-Hydroxy-1′-phenylethyl)-3-(diethoxymethyl)-4-hydroxymethylazetidin-2-one (34). Lactam **20** (557 mg, 1.75 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C. A 1 M solution of $LiBH_4$ (2.6 mL, 2.6 mmol) was then added dropwise while the temperature was maintained. The mixture was stirred for 2 h at rt, and then the reaction was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried with Na_2SO_4. Purification on a silica gel column using 2% MeOH in DCM as the eluent afforded product **34** (480 mg) (85%) as a light yellow oil: $[\alpha]_D$ −14 (*c* 0.61, $CHCl_3$); IR (film) ν 3262, 1760 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.97 (d, *J* = 4.6 Hz, 1H), 4.67 (dd, *J* = 4.0, 8.4 Hz, 1H), 4.45 (bs, 1H), 3.99 (dd, *J* = 8.5, 12.2 Hz, 1H), 3.95−3.87 (m, 1H), 3.87−3.81 (m, 1H), 3.81−3.66 (m, 5H), 3.61−3.52 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 166.9, 137.0, 128.8, 128.3, 127.5, 100.0, 65.2, 64.1, 64.0, 61.8, 60.2, 56.8, 55.2, 15.2; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{17}H_{25}NO_5Na$ 346.1630, found 346.1620

(1′*S*,3*S*,4*S*)-*N*-(2′-*tert*-Butyldimethylsiloxy-1′-phenylethyl)-3-(diethoxymethyl)-4-*tert*-butyldimethylsiloxymethylazetidin-2-one (35). Compound **34** (440 mg, 1.36 mmol) and imidazole (823 mg, 12.1 mmol) were dissolved in dichloromethane (7 mL), and a solution of TBDMSCl (569 mg, 3.76 mmol) in dichloromethane was added. The mixture was stirred at rt for 12 h followed by washing with water (5 mL). The organic phase was dried with Na_2SO_4 and purified on a silica gel column using hexane/ethyl acetate from 95:5 to 90:10 v/v as the eluents to afford 0.72 g (96%) as a colorless oil: $[\alpha]_D$ −13 (*c* 1.28, $CHCl_3$); IR (film) ν 1754 cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) δ 7.43−7.40 (m, 2H), 7.30−7.26 (m, 2H), 7.25−7.21 (m, 1H), 4.81 (d, *J* = 6.1 Hz, 1H), 4.56 (dd, *J* = 5.8, 9.4 Hz, 1H), 4.31 (dd, *J* = 9.4, 10.1 Hz, 1H), 3.92- 3.87 (m, 1H), 3.80 (dd, *J* = 5.8, 10.1 Hz, 1H), 3.78−3.75 (m, 2H), 3.74−3.65 (m, 2H), 3.62−3.51 (m, 2H), 3.47−3.44 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H), −0.08 (s, 3H), −0.10 (s,3H); ^{13}C NMR (150 MHz $CDCl_3$) δ 166.3, 138.3, 128.3, 127.9, 127.4, 99.0, 64.2, 63.1, 62.6, 62.2, 62.1, 57.6, 54.3, 25.9, 25.8, 18.2, 18.1, 15.3, −5.4, −5.5, −5.7, −5.8; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{29}H_{53}NO_5NaSi_2$ 574.3360, found 574.3356

(3*S*,4*S*) 3-(Diethoxymethyl)-4-*tert*-butyldimethylsiloxymethylazetidin-2-one (36). Lithium (50 mg, 7.1 mmol) was dissolved in dry ammonia (15 mL) at −78 °C and treated with a solution of compound **35** (252 mg, 0.46 mmol) in dry THF (1 mL) dropwise. The mixture was stirred at −78 °C for 1.5 h, the reaction was quenched with NH_4Cl (450 mg, 8.41 mmol), ammonia was allowed to evaporate off, and then THF was removed under reduced pressure. Ethyl acetate was then added, the mixture was stirred for 1 h, and the precipitate was filtered off. The organic phase was evaporated to give the crude product, which was purified on a silica gel column using hexane/ethyl acetate 6:4 as the eluent to afford 89 mg (61%) as a colorless oil: $[\alpha]_D$ +32 (*c* 0.45, $CHCl_3$); IR (film) ν 3392, 1732 cm^{-1}; ^1H NMR (400 MHz acetone-d_6) δ 7.20 (bs, 1H), 4.91 (d, *J* = 6.6 Hz, 1H), 3.96 (dd, *J* = 3.6, 10.8 Hz, 1H), 3.87 (dd, *J* = 7.1, 10.8 Hz), 3.72 (ddd, *J* = 3.6, 5.7, 7.1 Hz, 1H), 3.70−3.58 (m, 3H), 3.57−3.48 (m, 1H), 3.45 (ddd, *J* = 1.5, 5.7, 6.6 Hz, 1H), 1,15 (2*t*, *J* = 7.1 Hz, 2 × 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz acetone-d_6) δ 166.0, 98.8, 63.3, 62.0, 61.2, 56.2, 51.4, 25.4, 17.9, 14.8, −6.1; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{15}H_{31}NO_4NaSi$ 340.1920, found 340.1913.

(3*S*,4*S*)-*N*-(2′-Hydroxy-1′-phenylethyl)-4-methoxycarbonyl-3-(2″-methoxycarbonylbenzamide)azetidin-2-one (45). A solution of **24** (58 mg, 0,160 mmol) in THF (3 mL) was cooled to 0 °C and treated dropwise with a solution of lithium hydroxide monohydrate (8 mg, 0,32 mmol) in water (1,5 mL). The solution was stirred for 1 h at rt. Subsequently, an additional portion of lithium hydroxide monohydrate (6,6 mg, 0.16 mmol) was added, and the mixture was stirred for another 2 h to show total conversion of the substrate (TLC). The mixture was then acidified to pH = 1 with 1 M HCl to afford the diacid which was extracted with ethyl acetate (3 × 10 mL). The combined organic solutions were washed with brine (3 mL), dried with sodium sulfate (Na_2SO_4), and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), cooled to −30 °C, and treated with an excess of diazomethane. Subsequently, acetic acid (0,5 mL) was added, and the mixture was washed with water (2 mL) and brine (2 mL) and dried with Na_2SO_4. After evaporation of the solvent, the residue was purified on a silica gel column using ethyl acetate/hexane 4:1 v/v as the eluent to afford **45**, 45 mg (66%), as a white solid: mp 131−133 °C; $[\alpha]_D$ +8 (*c* 0.49, $CHCl_3$); IR (film) ν 3314, 1750, 1731, 1671 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$) δ 7.89−7.86 (m, 1H), 7.56−7.47 (m, 2H), 7.45−7.42 (m, 1H), 7.39−7.32 (m, 3H), 7.25−7.21 (m, 2H), 6.80 (d, *J* = 9.5 Hz, 1H), 5.77 (dd, *J* = 5.2, 9.5 Hz, 1H), 4.87 (dd, *J* = 3.8, 8.9 Hz, 1H), 4.40 (d, *J* = 5.2 Hz, 1H), 4.05 (dd, *J* = 8.9, 12.4 Hz, 1H), 3.88 (dd, *J* = 3.8, 12.4 Hz, 1H), 3.87 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ 170.9, 169.1, 166.7, 166.6, 136.6, 134.7, 132.0, 130.3, 130.2, 129.3, 129.0, 128.8, 127.9, 127.5, 63.0, 61,1, 58,6, 57.8, 53.0, 52.3; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{22}H_{22}N_2O_7$ 449.1325, found 449.1321

(1′*S*,3*S*,4*S*)-*N*-(2′-Hydroxy-1′-phenylethyl)-4-hydroxymethyl-3-*N*-(1″-hydroxyisoindoline-3″-one)azetidin-2-one (37) and Triacetates 38. Lactam **24** (0.11 g, 0.31 mmol) was dissolved in dry THF (6 mL) and cooled to 0 °C. Subsequently, a 0.25 M solution of $LiBH_4$ in dry THF (1.9 mL, 0.48 mmol) cooled to 0 °C was added dropwise with stirring at rt. The mixture was stirred for 5 h until total conversion of the substrate (TLC). The reaction was quenched with a saturated solution of ammonium chloride (7 mL) and water (3 mL). The mixture was then extracted with ethyl acetate (30 + 10 + 10 mL), and the organic phase was washed with brine (10 mL), dried, and evaporated. The crude **37** was dissolved in Et_3N (7 mL) and treated with acetic anhydride (0.20 mL). The mixture was stirred for 1.5 h, and then ethyl acetate (30 mL) and water (10 mL) were added. The organic phase was washed with brine (10 mL), dried with Na_2SO_4, and evaporated. Purification on a silica gel column using hexane/ethyl acetate 1:1 v/v as the eluent to afford 124 mg (82%) of a mixture of (1″*R*) and (*S*)-diastereomers **38**.

Diastereomer **38**(1″*S*): mp 39−42 °C; $[\alpha]_D$ + 73 (*c* 0.64, DCM); IR (film) ν 1763, 1742, 1723 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80−7.77 (m, 1H), 7.61−7.56 (m, 2H), 7.55−7.51 (m, 1H), 7.42−7.36 (m, 4H), 7.35−7.31 (m, 1H), 7.20 (s, 1H), 5.19 (d, *J* = 3.7 Hz, 1H), 4.82 (dd, *J* = 5.1, 9.9 Hz, 1H), 4.69 (dd, *J* = 9.9, 11.4 Hz, 1H), 4.49 (dd, *J* = 5.1, 11.4 Hz, 1H), 4.27 (dd, *J* = 8.2, 11.9 Hz, 1H), 4.15 (dd, *J* = 4.5, 11.9 Hz, 1H), 4.07 (ddd, *J* = 3.7, 4.5, 8.2 Hz, 1H), 2.10 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.2, 170.1, 168.2, 163.7, 141.7, 136.0, 133.3, 130.5, 130.1, 129.1, 128.7, 127.6, 124.6, 123.8, 80.9, 63.9, 63.8, 58.5, 58.4, 57.3, 20.8 × 2, 20.6; HRMS (ESI-TOF) *m*/*z* calcd for $[M + Na^+]$ $C_{26}H_{26}N_2O_8Na$ 517.1587, found 517.1591

Diastereomer **38**(1″*R*): mp 151−153 °C; $[\alpha]_D$ +26 (*c* 0.41, DCM); IR (film) ν 1766, 1742, 1724 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81−7.78 (m, 1H), 7.61−7.57 (m, 1H), 7.56−7.52 (m, 1H),

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7.51−7.48 (m, 1H) 7.41−7.39 (m, 4H), 7.36−7.32 (m, 1H), 7.04 (s, 1H), 5.11 (d, J = 4.8 Hz, 1H), 5.02 (dd, J = 5.4, 9.8 Hz, 1H), 4.74 (dd, J = 9.8, 11.5 Hz, 1H), 4.50 (dd, J = 5.4, 11.5 Hz, 1H), 4.37 (dd, J = 3.0, 12.2 Hz, 1H), 4.07 (dd, J = 7.7, 12.2 Hz, 1H), 3.89 (ddd, J = 3.0, 4.8, 7.7 Hz, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (150 MHz $CDCl_3$) δ 171.3, 171.0, 170.0, 168.1, 164, 141.0, 135.4, 133.2, 130.6 × 2, 129.0, 128.6, 127.6, 124.0, 123.8, 82.2, 63.6, 63.2, 60.1, 57.5, 56.8, 21.0, 20.9, 20.6; HRMS (ESI-TOF) m/z calcd for [M + Na^+] $C_{26}H_{26}N_2O_8Na$ 517.1587, found 517.1579

(1″*R*,3*S*,4*S*)-*N*-(2′-*tert*-Butyldimethylsiloxy-1′-phenylethyl)-4-*tert*-butyldimethylsiloxymethyl-3-*N*-(1″-hydroxyisoindoline-3″-one)azetidin-2-ones (39). Lactam **24** (263 mg, 0.73 mmol) was dissolved in 10 mL of dry THF and cooled to 0 °C. Subsequently, a solution of $LiBH_4$ (1 M in THF) was added dropwise, and the mixture was stirred at rt for 3 h. The reaction was quenched with a saturated solution of NH_4Cl (20 mL). After extraction with ethyl acetate (3× 50 mL), the organic phases were combined and dried with Na_2SO_4. The crude product was purified on a silica gel column using 0−5% methanol in DCM to afford 213 mg (80%) of a white foam, which was used for the next step without purification.

The crude product (213 mg, 0.58 mmol) obtained in the previous reaction was dissolved in 10 mL of DCM, and imidazole (200 mg, 2.94 mmol) was added followed by *tert*-butyldimethylsilyl chloride (195 mg, 1.28 mmol) in 5 mL of DCM. The mixture was stirred for 3 h at rt, and then the reaction was quenched by the addition of 15 mL of water and vigorous stirring. After that, the phases were separated. The organic phase was dried with Na_2SO_4 and evaporated. The crude product was purified on a silica gel column using ethyl acetate−hexane 1:4 v/v as the eluent to afford **39** 156 mg (45%) of a colorless oil: IR (film) ν 3357, 1756, 1745, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.8−7.3 (m, 10H), 6.19 (bs, 0.6H), 6.06 (d, 0.4H, J = 4.6 Hz), 5.17 (d, 0.6H, J = 5.0 Hz), 5.14 (bd, 0.4H, J = 3.4 Hz), 4.64 (dd, 0.6H, J = 5.2, 9.5 Hz), 4.57 (dd, 0.4H, J = 5.7, 8.5 Hz), 4.37 (dd, 0.6H, J = 9.5, 10.6 Hz), 4.30 (dd, 0.4H, J = 8.6, 10.2 Hz), 4.05(m, 0.4H), 4.01 (m, 0.6H), 3.88−3.83 (m, 2H), 3.81 (dd, 0.6, J = 4.0, 11.4 Hz), 3.68 (dd, 0.4H, J = 4.2, 11.3 Hz); ^{13}C NMR ($CDCl_3$) δ 167.9, 167.8, 165.8, 165.1, 144.4, 143.8, 137.1, 137.0, 132.7, 132.5, 131.2, 130.6, 129.7, 128.7, 128.6, 128.1, 127.9, 127.8 × 2, 127.7, 123.5 × 2, 123.41, 123.36, 83.0, 81.1, 64.4, 64.3, 62.3, 62.0, 61.9, 61.2, 61.1, 60.9, 58.7, 58.1, 25.82, 25.79, 25.70, 25.67, 18.3, 18.2, 18.14, 18.12, −5.41, −5.43, −5.5, −5.6, −5.7, −5.8, −6.0, −6.1; HRMS (ESI-TOF) m/z calcd for [M + Na^+] $C_{32}H_{48}N_2O_5NaSi_2$ 619.2999, found 619.2998

(3*S*,4*S*)-*N*-(2′-*tert*-Butyldimethylsiloxy-1′-phenylethyl)-4-*tert*-butyldimethylsiloxymethyl-3-*N*-phthaloyl)azetidin-2-one (40). Compound **39** (156 mg, 0.26 mmol) was dissolved in 5 mL of DCM, manganese dioxide (680 mg, 7.82 mmol) was added, and the mixture was stirred under reflux for 3 h. Subsequently, the precipitate was filtered off. After evaporation of the solvent under reduced pressure, the crude product was purified on a silica gel column using ethyl acetate/hexane 15:85 v/v as the eluent to afford **40**, 123 mg (79%), as a colorless syrup: $[\alpha]_D$ −5 (c 0.64, DCM); IR (film) ν 1766, 1723 cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$) δ 7.88−7.83 (m, 2H), 7.76−7.70 (m, 2H), 7.53−7.47 (m, 2H), 7.41−7.36 (m, 2H), 7.32−7.27 (m, 1H), 5.40 (d, J = 5.2 Hz, 1H), 4.60 (dd, J = 5.7, 8.6 Hz, 1H), 4.37 (dd, J = 8.7, 10.4 Hz, 1H), 4.40 (ddd, J = 5.2, 6.2, 7.4 Hz, 1H), 3.89 (dd, J = 5.7, 10.4 Hz, 1H), 3.72 (dd, J = 6.2, 10.6 Hz, 1H), 3.58 (dd, J = 7.4, 10. Hz, 1H), 0.89 (s, 9H), 0.64 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H), −0.24 (s, 3H), −0.32 (s, 3H); ^{13}C NMR (125 MH $CDCl_3$) δ 167.4, 164.0, 137.6, 134.3, 131.8, 128.6, 127.8, 127.6, 123.6, 64.4, 62.5, 62.2, 60.5, 55.0, 25.8, 25.5, 18.2, 17.9, −5.4, −5.5, −5.9, −6.0; HRMS (ESI-TOF) m/z calcd for [M + Na^+] $C_{32}H_{46}N_2O_5NaSi_2$ 617.2843, found 617.2839

(3*S*,4*S*)-4-(*p*-Methoxyacetophen-2-oxycarbonyl)-3-*N*-phthaloylazetidin-2-one (42). Lactam **28** (100 mg, 0.26 mmol) was dissolved in acetonitrile (6 mL) and cooled to 0 °C. At this temperature, cerium ammonium nitrate (1,18 g, 2.15 mmol) in water (3 mL) was added. The mixture was stirred at rt for 2.5 h. After that, it was extracted with ethyl acetate (15, 10, 10 mL). The combined organic phases were washed with a saturated solution of sodium bicarbonate (15 mL), dried with sodium sulfate, and evaporated. The crude product was purified on a silica gel column using hexane/ethyl acetate 1:1−0:1 v/v as the eluent to give product **42** (43 mg) (41% yield) as a light yellow solid: mp 92−94 °C; $[\alpha]_D$ +80 (c 0.98, acetone); IR (film) ν 1793, 1764, 1717, 1694 cm^{-1}; ^{1}H NMR (400 MHz acetone-d_6) δ 8.13 (br s, 1H), 7.89−7.87 (m, 4H), 7.79−7.74 (m, 2H), 6.98−6.93 (m, 2H), 5.78 (d, J = 5.8 Hz, 1H), 5.35 (d, J = 16.3 Hz, 1H), 5.22 (d, J = 16.3, 1H), 4.86 (d, J = 5.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz aceton-d_6) δ 189.5, 167.7, 166.7, 164.0, 163.6, 134.5, 132.0, 129.9, 127.0, 123.3, 113.9, 66.4, 57.6, 55.1, 53.3; HRMS (ESI-TOF) m/z calcd for [M + Na^+] $C_{21}H_{16}N_2O_7Na$ 431.0855, found 431.0857.

(3*S*,4*S*)-4-Hydroxymethyl-3-*N*-phthaloylazetidin-2-one (44). Compound **42** (142 mg, 0.35 mmol) was dissolved in dry THF (4 mL) and cooled to 0 °C. Subsequently, a 1 M solution of $LiBH_4$ was slowly added. The mixture was stirred at rt for 2.5 h. The reaction was then quenched with a saturated solution of NH_4Cl and stirred for 15 min. The mixture was extracted with ethyl acetate until TLC (5% methanol in ethyl acetate) of the aqueous phase did not indicate the presence of the product. The combined organic phases were dried with Na_2SO_4 and evaporated. Purification of the product on a silica gel column using ethyl acetate/methanol 95:5 v/v as the eluent to give 60 mg of **43** which subsequently was dissolved in 5 mL of acetone and treated with manganese dioxide (430 mg, 4.94 mmol). The suspension was refluxed for 2 h, additional manganese dioxide (188 mg, 2.16 mmol) was added, and reflux was continued for an additional 0.5 h. Subsequently, the mixture was filtered through Celite and evaporated. Purification on a silica gel column gave 16 mg of **44** (19% yield) as a white powder: mp 140−141 °C; $[\alpha]_D$ −4 (c 0.16, CH_3OH); IR (film) ν 1779, 1718 cm^{-1}; ^{1}H NMR (500 MHz aceton-d_6/D_2O) δ 7.90 (br, 4H), 5.39 (d, J = 5.3 Hz, 1H), 4.04 (m, 1H), 3.78 (dd, J = 6.7, 11.2 Hz, 1H), 3.64 (dd, J = 6.7, 11.2 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.3, 164.0, 134.5, 131.8, 123.2, 61.7, 56.6, 54.9; HRMS (ESI-TOF) m/z calcd for [M + Na^+] $C_{12}H_{10}N_2O_4Na$ 269.0538, found 269.0543.

(3*S*,4*S*)-4-*tert*-Butyldimethylsiloxymethyl-3-*N*-(2′-carbamoylbenzoyl)azetidin-2-one (41). Ammonia (20 mL) was condensed at −78 °C, and sodium (83 mg, 3.6 mmol) was added. The resulting blue solution was warmed, and the thus dried ammonia was recondensed at −78 °C. A solution of compound **40** (235 mg, 0.396 mmol) in THF (1.8 mL) was added via syringe to a solution of lithium (30 mg, 4.32 mmol) in dry liquid ammonia cooled to −78 °C. After 25 min, the reaction was quenched by the addition of solid ammonium chloride (0.34 g). The reaction mixture was slowly warmed to ambient temperature, and after the evaporation of ammonia, ethyl acetate (10 mL) was added and the mixture was stirred for 2 h. The solids were filtered off, and the solvent was removed to afford a mixture of compounds (0.238 g) as a yellow foam. Column chromatography on a silica gel column using ethyl acetate/hexane 9:1 followed by ethyl acetate/methanol 4:1 v/v as the eluents to give 40 mg of compound **39** (17%) and 15 mg of **41** (10%). **41**: colorless oil; $[\alpha]_D$ +27.9 (c 0.34, CH_3OH); IR ($CHCl_3$) ν 3302, 1753, 1705, 1672 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 0.03, 0.08 (2s, 6H, 2 × Me), 0.82 (s, 9H, *t*-Bu) 3.89 (dd, 1H, J = 4.7 and 11.2 Hz), 3.93−3.97 (m, 1H)-3.99 (dd, 1H, J = 2.9 and 11.2 Hz), 5.44 (d, 1H, J = 5.0 Hz) 7.51- 7.66 (m, 4H, Ar); ^{13}C NMR (150 MHz, acetone-d_6) δ 171.5, 170.3, 169.4, 135.4, 134.9, 130.1, 130.0, 127.7 127.5, 62.0, 57.2, 54.6, 25.0, 24.9, 24.8, 17.5, −6.8, −6.8; HRMS (ESI-TOF) m/z calcd for [M + Na]$^+$ $C_{18}H_{27}N_3O_4NaSi$ 400.1669, found 400.1663.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01979.

^{1}H and ^{13}C NMR spectra for selected compounds (PDF)

X-ray crystallographic data for compound **24** (CIF)

X-ray crystallographic data for compound **29** (CIF)

X-ray crystallographic data for compound **30** (CIF)

X-ray crystallographic data for compound **32** (CIF)

X-ray crystallographic data for compound **(1″*R*)-38** (CIF)

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Notes

The authors declare no competing financial interest.

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