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Tetrahedron: *Asymmetry*

Asymmetric inverse electron-demand 1,3-dipolar cycloaddition of ynolates with a chiral nitrone derived from L-serine leading to β-amino acid derivatives

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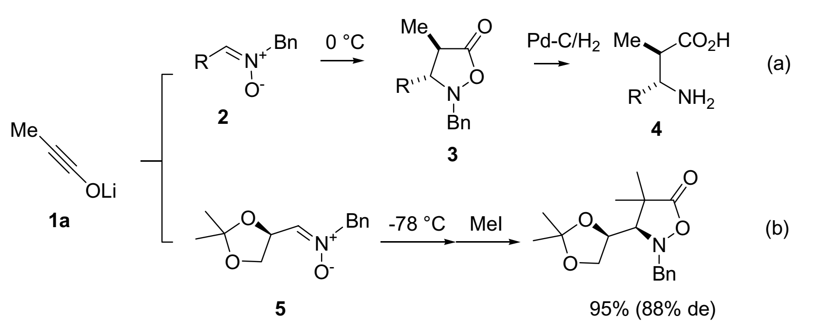
Abstract—Asymmetric 1,3-dipolar cycloaddition of lithium ynolates with a nitrone derived from Garner's aldehyde is described. The cycloadducts, 5-isoxazolidinones, were obtained in good yields with high diastereoselectivity. Alkylation of the intermediates, the 5-isoxazolidinone enolates, was also achieved with high selectivity, the products of which were converted into the enantiomerically pure β-amino acids, β-lactams, and γ-lactams. In our cycloaddition, lithium ynolates proved to be much better as nucleophiles than lithium enolates.

1. Introduction

Ynolates **1** are a versatile reactive species with an electron-rich triple bond,[1] however, asymmetric reactions of ynolates still remain unexplored. If a wider selection of asymmetric syntheses using these compounds could be developed, ynolates would then become a more powerful tool in the synthetic chemist's arsenal. Since our development of a new synthetic method for ynolates,[2] we have found that the anionic inverse electron-demand 1,3-dipolar cycloaddition of nitrones **2** with ynolates **1** gives 5-isoxazolidinones **3** [Scheme 1(a)].[3] As the products can be easily converted into β-amino acids **4**, we were eager to extend the method to asymmetric reactions. Recently, we reported the asymmetric 1,3-dipolar cycloaddition of ynolates with the D-mannitol-derived chiral nitrone **5** with an oxygen-based stereogenic center.[4]

While good diastereoselectivity was achieved using this nitrone, various kinds of asymmetric reactions of ynolates would have to be conducted to demonstrate the potential usefulness of ynolates in asymmetric reactions. Products which contain a nitrogen functionality would



Scheme 1.

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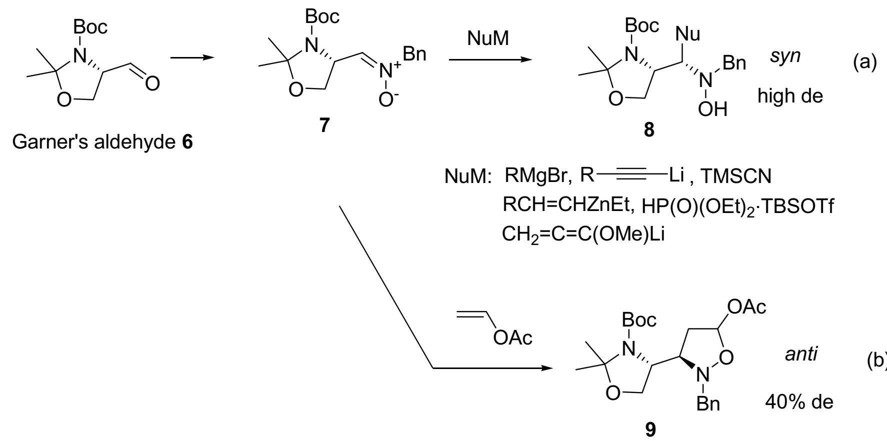


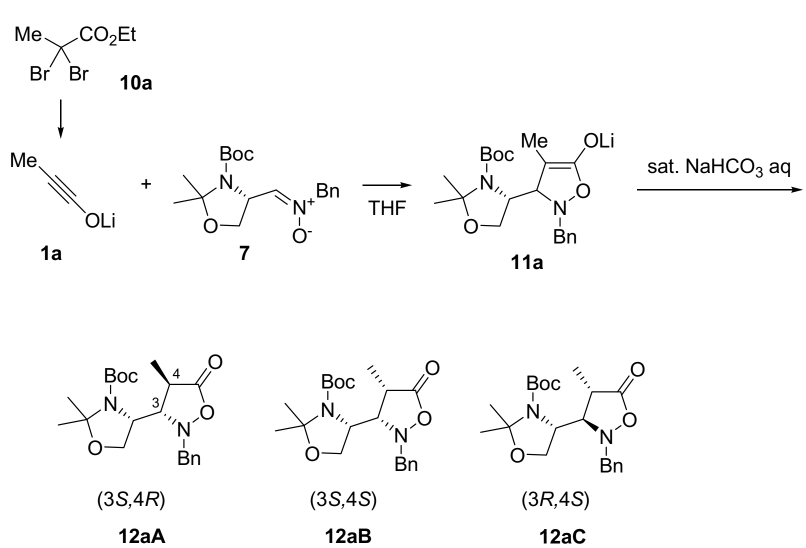
Scheme 2.

be more valuable for the construction of bioactive organic molecules. Garner's aldehyde **6**, readily prepared from L-serine, is a valuable chiral building block which is configurationally stable and has been used extensively in asymmetric synthesis.[5] Nitrone **7** derived from Garner's aldehyde **6** is also a good chiral building block, particularly for construction of chiral diamines. In fact, the addition of Grignard reagents,[6] lithium acetylides,[7] vinylzinc,[8] silyl cyanides,[9] diethyl phosphite[10] and allenyl lithium[11] afforded the *syn*-adducts **8** with excellent diastereoselectivity [Scheme 2(a)]. However, successful additions of metal ester enolates have not been reported.[12] 1,3-Dipolar cycloadditions of **7**, the most representative reaction of nitrones, have been reported only once using vinyl acetate as a dipolarophile to give the *anti*-adduct **9** with moderate diastereoselectivity [Scheme 2(b)].[12] Thus, the asymmetric cycloaddition of **7** with dipolarophiles still remains unexplored. We herein report the asymmetric 1,3-dipolar cycloaddition of ynolates with the chiral nitrone **7** leading to chiral building blocks bearing an amino substituent.

2. Results

2.1. Asymmetric cycloaddition

Lithium ynolate **1a**, prepared from dibromo ester **10a**[13] with *t*-BuLi, reacted with the nitrone **7** at −78 °C to afford desired 5-isoxazolidinone **12a** in 32% yield after quenching with aqueous $NaHCO_3$ solution, along with 68% recovery of **7** (Scheme 3: Table 1, entry 1). After separation of the stereoisomers by silica gel column chromatography, the diastereomeric ratio (**12aA**:**12aB**:**12aC**) was found to be 73:21:6. Due to broadening in the ^1H NMR spectrum, the relative configuration of the major isomer **12aA** could not be determined at this stage, but it was shown to be (3*S*,4*R*) by the transformation to the β- and γ-lactams, described later. The configuration of **12aB** was determined to be (3*S*,4*S*) by X-ray crystal structure analysis, however that of the minor isomer **12aC** has yet to be ascertained, but it is possibly (3*R*,4*S*) rather than (3*R*,4*R*).[14] Consequently, the diastereofacial selectivity (3*S* vs 3*R*) of the addition to the



Scheme 3.

Table 1. Optimization of the reaction temperature for Scheme 3

Entry	Temperature (°C)	Time (h)	Yield (%)	**A**:**B**:**C**	de[a]
1	−78	2	32	73:21:6	88
2	−50	1	76	57:28:15	70
3	−20	1	66	72:23:5	90
4	0	1	95	71:24:5	90

[a] (**A** + **B**) versus **C**.

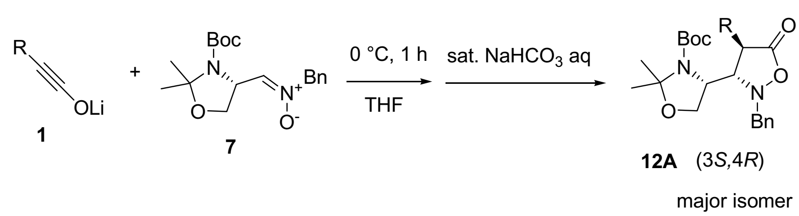
nitrone was 88% de. In order to improve the yield of the cycloadducts, the reaction was carried out at higher temperature. As shown in Table 1, the best yield of the adducts was obtained at 0 °C without the loss of diastereoselectivity.

Since the ratio of isomers **12aA** and **12aB** should be dependent on the quenching conditions, *tert*-butanol was added to the enolate solution at 0 °C in place of aqueous $NaHCO_3$ solution to convert the *cis*-isomer **12aB** into the thermodynamically more stable *trans*-isomer **12aA**. As expected, the isomer **12aB** disappeared, but the total yield of isomers **A** and **C** decreased to 73%. Quenching with acetic acid resulted in a 76:16:8 ratio of the isomers **A**, **B**, and **C** in 71% yield. Based on these results, we then employed the conditions for entry 4 (Table 1) in the following experiments.

We next examined the cycloadditions of several kinds of ynolates with nitrone **7**. As depicted in Table 2, cycloadducts **12A** were obtained in good yield with good to excellent diastereoselectivity. In the cases of entries 1 and 3, since there was only a small amount of the minor isomers, with no separation or isolation of the individual isomers **B** and **C** required. The sterically hindered ynolates **1c** and **1e** afforded cycloadducts **12A** without detection of minor isomers (entries 2 and 4). In the case of the trimethylsilyl substituted ynolate **1e**, the product was isolated after desilylation by citric acid (entry 4).

The enolates **11** of the 5-isoxazolidinones generated by the cycloaddition were alkylated to furnish the 2,2-disubstituted products **13** along with a small amount of unalkylated products **12A** (Table 3). In entry 1, the minor stereoisomers were not detected, although the C-3 minor isomer of enolate **11a** should have been present in ca. 5%. Unlike the protonation, since R is sterically hindered, the stereoselectivity as well as the yield

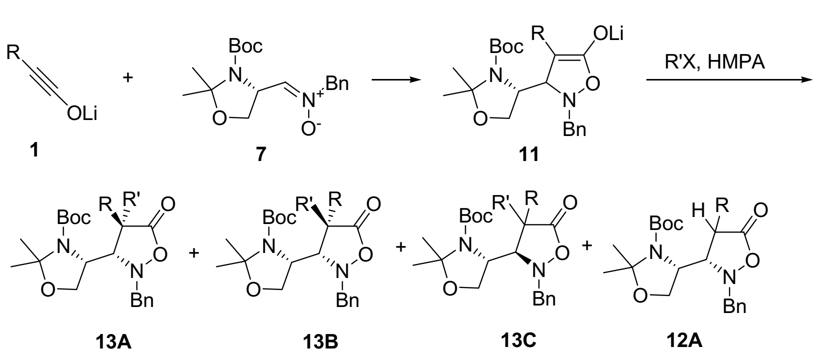
Table 2. Asymmetric cycloaddition of ynolates **1** with the nitrone **7**



Entry	Ynolate (R)		Yield (%)		Major : minors[a]
1	**1b**	Bu	**12bA**	85	90:10
2	**1c**	*i*-Pr	**12cA**	93	>99:1
3	**1d**	Ph	**12dA**	89	94:6
4	**1e**	TMS	**12eA**	92[b]	>99:1

[a] The sum of the minor isomers **B** and **C**, the ratio of which was not determined.
[b] After desilylation by citric acid (R = H in **12eA**).

Table 3. Alkylation of 5-isoxazolidinone enolates



Entry	R	R′X	Yield of major isomer (%)	Major : minors	**12A**
1	Me	MeI	**13aA**, 81	>99:1	3
2	Bu	MeI	**13bA**, 75	94:6	9
3	*i*-Pr	MeI	**13cA**, 43	71:29	24
4	Me	BnBr	**13aB**, 84	88:12	0

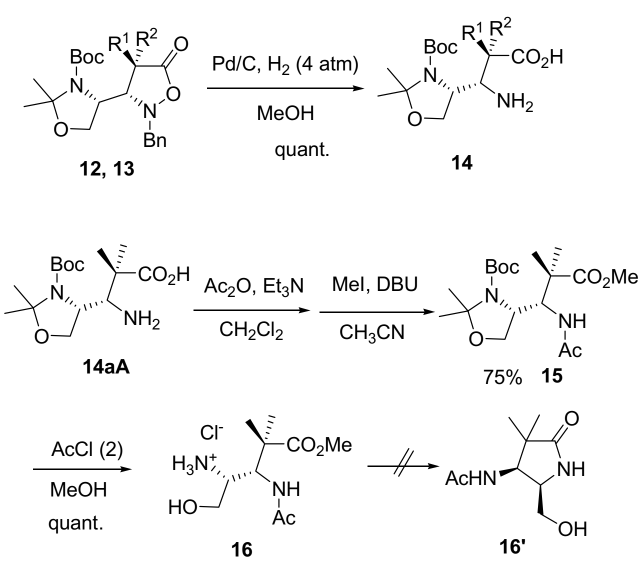
decreased (entry 3 vs Table 2, entry 2). The major isomers were generated by the attack of iodomethane on the α-face of the enolates (entries 2 and 3). However, benzyl bromide attacked predominantly from the β-face, in which case the benzyl bromide approached *trans* to the oxazoline moiety (entry 4). The stereochemistry of these compounds was determined by the transformation to γ-lactams (entry 3) or X-ray crystal structure analysis (entry 4).

Table 4. Transformation to β-lactams

Entry	R^1	R^2	**17** (%)		**18** (%)	
1	Me	H	**17a**	92	**18a**	98
2	Bu	H	**17b**	53	**18b**	58
3	*i*-Pr	H	**17c**	99	**18c**	61
4	Ph	H	**17d**	83	**18d**	76
5	Bu	Me	**17e**	67	**18e**	60
6	*i*-Pr	Me	**17f**	58	**18f**	76

2.2. Transformation to γ-lactams

In order to determine the stereochemistry and demonstrate the synthetic utility, we next tried to convert chiral 5-isoxazolidinones into γ-lactams (Scheme 4). The major isomers of the 5-isoxazolidinones **12** and **13** were reduced by Pd/C catalyzed hydrogenation to afford the β-amino acids **14** almost quantitatively. Acetylation of the amino group, followed by esterification, gave **15** in 75% yield. Removal of the acetonide and Boc group was carried out with 2 equiv of acetyl chloride in methanol to provide **16** quantitatively. However, attempts to cyclize to γ-lactam **16′** under basic conditions resulted in hydrolysis of the methyl ester or intramolecular transfer of the acetyl group. Attempts to protect the amino group of **14** with other *N*-protective groups such as CbzCl, benzoyl chloride, or tosyl chloride were unsuccessful, probably because of steric hindrance.

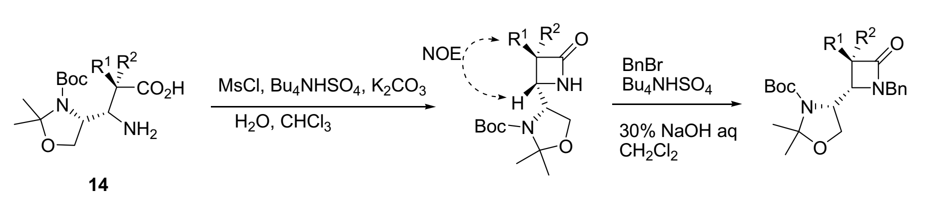


Scheme 4.

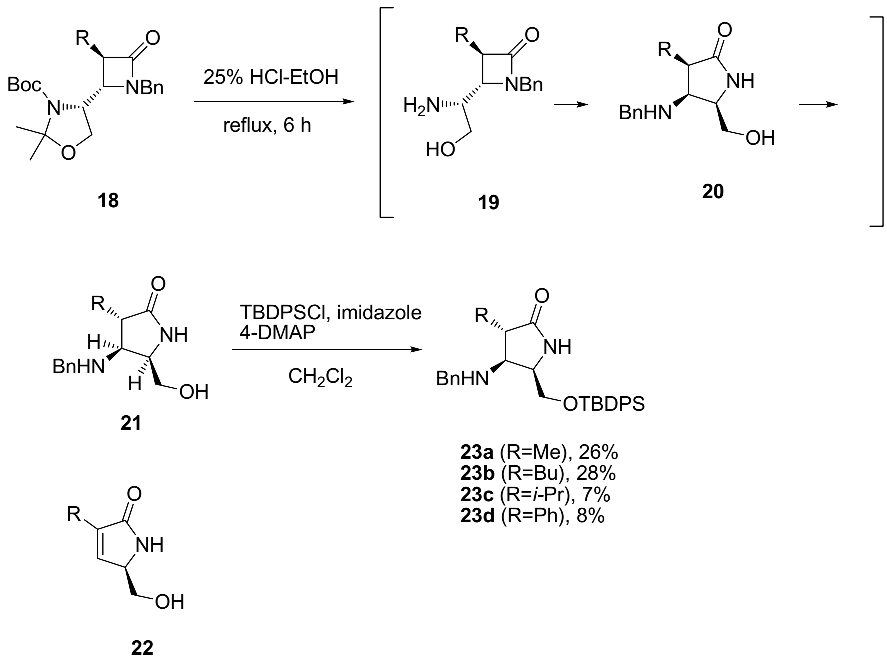
We then examined the transformation of β-amino acids **14** into γ-lactams through β-lactams **17** as shown in Scheme 5. According to the reported method,[15] the β-amino acids were converted to the β-lactams **17** in good yields (Table 4). The NOE experiments of **17** revealed the *cis*-relationship between R^1 and the C4–H.[16] The β-lactams were *N*-benzylated with benzyl bromide in good yields.[17]

Finally, we attempted the transformation to the γ-lactams under acidic conditions. The β-lactam **18a** was treated with acetyl chloride (5 equiv) in MeOH for 4 h under reflux to give the deprotected β-lactam **19a** in 79% yield. In the presence of 10 equiv of acetyl chloride in MeOH, the reaction was allowed to run for 16 h under reflux to afford 23% of the desired γ-lactam **20a** along with 56% of **19a**. To complete the conversion of **19a** to **20a**, it was found that the C3-epimerized γ-lactam **21a** was generated under harsher conditions. Since **20a** and **21a** were inseparable by column chromatography, we tried to completely convert **20a** to **21a**. Finally, when the β-lactams were refluxed in 25% HCl–EtOH for 6 h, cyclization, followed by epimerization, provided the γ-lactam **21a**, along with a small amount of the unsaturated γ-lactam **22a**. On prolonged reaction, **22a** was predominantly generated. In order to facilitate the separation of **21a** from **22a**, the mixture was treated with TBDPSCl to give the *O*-silylated γ-lactam **23a** in 26% overall yield and the nonsilylated **22a**, which were easily separated by column chromatography (Scheme 6). The same transformation was applied to **18b**,**c**, and **18d** to furnish **23b**,**c**, and **23d** in moderate yields.

Investigation of the stereochemistry of **23a** and **23b** by NOE difference spectroscopy revealed *cis*-relationships between the Me, C4–H and the C5–H as shown in Figure 1. According to these results, epimerization of C3–H during the acidic cyclization was also apparent. In **23c**, the NOE between C4–H and C5–H was not clear, due to overlapping of signals, but NOE experiments on the methylated γ-lactam **20f**, generated by the same protocol, disclosed the *cis*-relationship between C4–H and C5–H (Scheme 7). In the case of **23d**, although the C3 stereochemistry was ambiguous, the configuration of



Scheme 5.



Scheme 6.

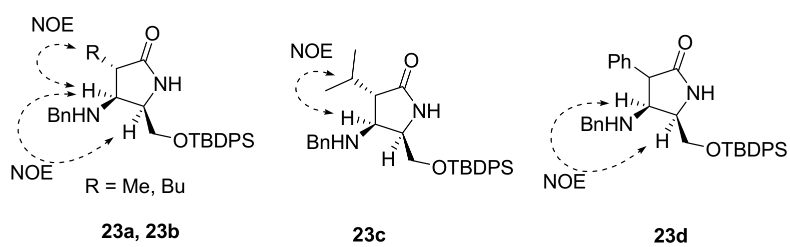
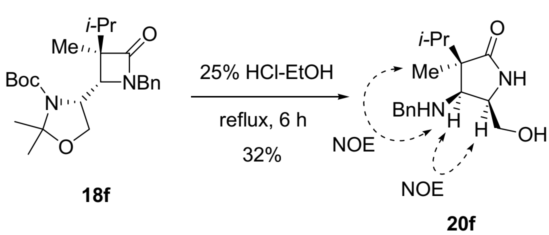


Figure 1. NOE experiments.



Scheme 7.

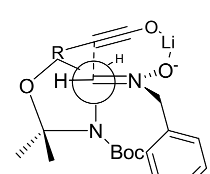


Figure 2.

C4 and C5 was found to be the same as that of the others by NOE experiments.

3. Discussion

Ynolates have been shown to have high diastereofacial selectivity as well as high reactivity with the nitrone **7**, derived from Garner's aldehyde. According to several reports[18,7b] on the addition of organometallic reagents to nitrone **7**, the stereochemical outcome would be as shown in Figure 2. In this transition state model, the electronegative group (NBoc) is perpendicular to the C=N bond while the proton (C*H*=N) occupies the inner position. The ynolate would attack the nitrone *anti* to the C–N(Boc) bond.

Since metal enolates of methyl acetate are much less reactive than ynolates,[12] we decided to add the lithium enolate of ethyl propionate to nitrone **7**. We obtained the 5-isoxazolidinone **12a** in 33% yield with a diastereomeric ratio of 62:38 (**12aA**:**12aC**). This is actually a worse yield than this for the ynolates, which are more compact nucleophiles, and hence allow for greater efficiency. This remarkable contrast demonstrates the high potential of ynolates in asymmetric reactions.

The C4 stereochemistry was determined in the protonation or alkylation of 5-isoxazolidinone enolates. Under either kinetic or thermodynamic protonation conditions, *cis*-protonation or alkylation predominated to give the *trans*-products, which would be thermodynamically more stable than the *cis*-products (Table 2, entries 1–3; Table 3, entries 1–3). Since the reaction center would be sp^3-like rather than sp^2 in the transition state, which would be relatively very product-like, the *trans*-products should be generated. Furthermore, the *N*-benzyl group, which may occupy the face opposite to the *N*-Boc-oxazolidine, would assist in the α-attack of the electrophiles (Fig. 3). In the benzylation (Table 3, entry 4) however, the larger electrophile group would avoid steric interference with the *N*-Boc-oxazolidine, and thus the opposite stereoselectivity would be achieved.

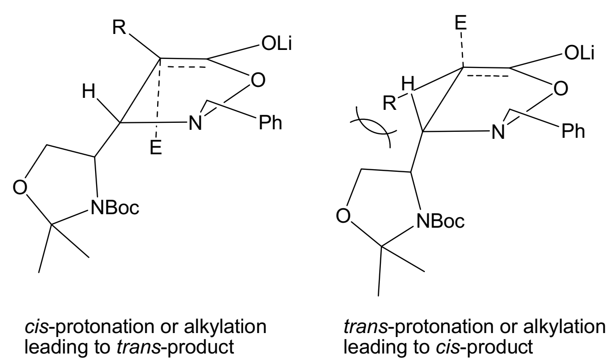


Figure 3. *cis*-protonation or alkylation leading to *trans*-product *trans*-protonation or alkylation leading to *cis*-product.

4. Conclusion

We have reported the highly stereoselective 1,3-dipolar cycloaddition of ynolates with Garner's aldehyde-derived nitrone to furnish the 3,4-disubstituted and 3,4,4-trisubstituted 5-isoxazolidinones. These adducts can then be taken onto the enantiomerically pure β-amino acids and γ-lactams, which are useful as chiral building blocks. Expanding on our previous report, we have also found that ynolates, and not enolates, demonstrated a greater possibility for high stereodifferentiation.

5. Experimental

5.1. General

THF was distilled from Na–benzophenone ketyl. ^{1}H NMR (JNM AL-400, 400 MHz) and ^{13}C NMR (JNM AL-300, 75 MHz and AL-400, 100 MHz) spectra were recorded in $CDCl_3$, unless otherwise noted, while chemical shifts (δ) are given in ppm relative to TMS (0.0 ppm). IR spectra: JASCO FTIR-410. Mass spectra: JEOL JMS-SX102A, JMS-DX303, JMS-AMSUN200, Waters LCT-premier. Column chromatography: Kanto silica gel. Preparative HPLC was performed using Mightysil Si60, Kanto. Analytical TLC: Silica gel 60 F_{254} plates, Merck. Optical rotation: JASCO P-1010. Melting point: Büchi 535. All reactions were performed under an Ar atmosphere, unless otherwise noted. The nitrone **7** was prepared by the procedure of Merino.[6] α,α-Dibromo esters were prepared using our procedure.[13]

5.2. Asymmetric cycloaddition

5.2.1. Representative procedure: (3*S*,4*R*)-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-2-benzyl-4-methylisoxazolidin-5-one 12aA. To a solution of ethyl 2,2-dibromopropanoate (312 mg, 1.2 mmol) in anhydrous THF (6 mL), cooled to −78 °C, was added dropwise a solution of *t*-BuLi (3.4 mL, 4.8 mmol, 1.44 M in pentane). The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, a solution of nitrone **7** (334 mg, 1.0 mmol) in THF (2 mL) was added to the colorless reaction mixture. After 1 h at 0 °C, a satd $NaHCO_3$ solution (20 mL) was added, and the mixture was stirred vigorously at rt. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (SiO_2; EtOAc–hexane, 1:9) afforded a mixture of the isomers (372 mg, 71:24:5, 95%) as a colorless oil. The major isomer **12aA** was separated from the mixture by HPLC. ^{1}H NMR (400 MHz, DMSO, 70 °C): δ = 1.21 (d, J = 6.8 Hz, 3H), 1.41 (s, 3H), 1.44 (s, 9H), 1.53 (s, 3H), 2.99 (dq, J = 6.8, 11.2 Hz, 1H), 3.67 (dd, J = 6.8, 11.2 Hz, 1H), 4.03 (ddd, J = 6.8, 6.8, 9.6 Hz, 1H), 4.04 (d, J = 14.4 Hz, 1H), 4.09 (br s, 1H), 4.23 (dd, J = 1.6, 9.6 Hz, 1H), 4.29 (d, J = 14.4 Hz, 1H), 7.28–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7, 16.2, 22.0, 23.5, 25.7, 26.5, 28.2, 28.4 , 37.8, 56.3, 56.7, 63.3, 63.4, 63.7, 70.8, 72.2, 80.7, 81.0, 94.4, 95.1, 127.8, 128.1, 128.4, 128.5, 128.9, 129.0, 134.9, 135.2, 151.8, 152.8, 176.2; IR (neat): 1778, 1696 cm^{-1}; MS (EI): m/z = 390 (M^+), 57 (100%); HRMS (EI): m/z calcd for $C_{21}H_{30}N_2O_5$, 390.2155. Found: 390.2168. $[\alpha]_D^{23}$ = −93.9 (c 1.16, $CHCl_3$).

5.2.2. (3*S*,4*S*)-2-Benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-methylisoxazolidin-5-one 12aB. Colorless prisms, mp 139–140 °C (ether/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, J = 7.1 Hz, 3H), 1.50 (s, 9H), 1.56 (s, 3H), 1.62 (s, 3H), 2.72 (br, 1H), 3.59 (br, 1H), 3.94 (br s, 1H), 4.03 (dd, J = 7.1, 9 Hz, 1H), 4.26 (br, 1H), 4.28 (dd, J = 1.7, 9 Hz, 1H), 4.42 (d, J = 14 Hz, 1H), 7.27–7.42 (m, 5H), IR ($CHCl_3$): 1773, 1688 cm^{-1}. Anal. Calcd for $C_{21}H_{30}N_2O_5$, C, 64.59; H, 7.74; N, 7.17. Found: C, 64.29; H, 7.58; N, 7.11; $[\alpha]_D^{25}$ = −90.2 (c 1.05, $CHCl_3$). Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-273643. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

5.2.3. (3*S*,4*R*)-2-Benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-butylisoxazolidin-5-one 12bA. Colorless oil; purified by preparative HPLC (EtOAc–

hexane, 1:9); ^{1}H NMR (400 MHz, DMSO, 80 °C): $\delta = 0.86$ (t, $J = 6.8$ Hz, 3H), 1.25 (m, 2H), 1.41 (s, 3H), 1.43 (s, 9H), 1.52 (s, 3H), 1.41–1.61 (m, 4H), 2.93 (dt, $J = 6.0$, 8.4 Hz, 1H), 3.78 (br s, 1H), 4.03–4.12 (m, 3H), 4.08 (d, $J = 14$ Hz, 1H), 4.27 (d, $J = 14$ Hz, 1H), 7.28–7.35 (m, 5H); ^{13}C NMR (75 MHz, DMSO): $\delta = 13.7$, 21.8, 22.20, 22.25, 23.4, 25.6, 26.4, 27.6, 27.8, 29.2, 29.6, 41.7, 56.2, 56.5, 62.5, 63.0, 63.4, 66.3, 67.5, 79.1, 79.8, 93.7, 93.9, 127.5, 127.6, 128.20, 128.28, 129.0, 129.1, 135.9, 151.5, 152.1, 176.00, 176.09; IR (neat): 1774, 1694 cm^{-1}; MS (EI): $m/z = 432$ (M$^+$), 91 (100%); HRMS (EI): m/z calcd for $C_{24}H_{36}N_2O_5$, 432.2626. Found: 432.2644. $[\alpha]_D^{24} = -119.1$ (c 1.16, $CHCl_3$).

5.2.4. (3*S*,4*R*)-2-Benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-isopropylisoxazolidin-5-one 12cA. Colorless oil; purified by preparative HPLC (EtOAc–hexane, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$, 1.07 (d, $J = 6.0$ Hz, 3H × 2), 1.12, 1.18 (d, $J = 6.0$ Hz, 3H × 2), 1.42, 1.44 (s, 3H × 2), 1.48 (s, 9H), 1.58, 1.61(s, 3H × 2), 1.89 (br s, 1H), 2.98 (m, 1H), 3.79 (br s, 1H), 4.02–4.25 (m, 5H), 7.33 (br s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.9$, 18.0, 20.3, 20.5, 22.0, 23.4, 25.9, 26.7, 28.2, 28.4, 29.8, 47.7, 57.6, 58.1, 63.7, 64.1, 65.4, 66.8, 80.5, 80.9, 94.4, 95.0, 127.8, 128.1, 128.4, 128.6, 128.8, 129.2, 135.2, 152.8, 175.2, 175.6; IR (neat): 1771, 1702 cm^{-1}; MS (EI): $m/z = 416$ (M$^+$), 57 (100%); HRMS (EI): m/z calcd for $C_{23}H_{34}N_2O_5$, 418.2468. Found: 418.2451. $[\alpha]_D^{23} = -125.2$ (c 0.95, $CHCl_3$).

5.2.5. (3*S*,4*R*)-2-Benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-phenylisoxazolidin-5-one 12dA. Colorless oil; purified by preparative HPLC (EtOAc–hexane, 1:9); ^{1}H NMR (400 MHz, DMSO, 80 °C): $\delta = 1.01$ (s, 3H), 1.31 (s, 3H), 1.34 (s, 9H), 4.04 (dd, $J = 7.0$, 10.0 Hz, 1H), 4.20 (d, $J = 14.4$ Hz, 1H; m, 1H), 4.31 (t, $J = 10.0$ Hz, 1H; m, 1H), 4.42 (d, $J = 14.4$ Hz, 1H; m, 1H), 7.28–7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.4$, 25.6, 28.2, 48.8, 56.8, 63.0, 63.1, 68.4, 80.7, 94.3, 127.8, 128.2, 128.3, 128.6, 128.8, 129.0, 134.4, 135.1, 152.4, 173.4; IR (neat): 1778, 1689 cm^{-1}; MS (EI): $m/z = 452$ (M$^+$), 91 (100%); HRMS (EI): m/z calcd for $C_{26}H_{32}N_2O_5$, 452.2311. Found: 452.2311. $[\alpha]_D^{23} = -86.4$ (c 1.34, $CHCl_3$).

5.2.6. (3*S*)-2-Benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-isoxazolidin-5-one 12eA′. To a solution of the crude mixture of (3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-2-benzyl-4-trimethylsilylisoxazolidin-5-one) in THF (4.5 mL) and H_2O (1.5 mL) was added citric acid (768 mg, 4 mmol) and the mixture stirred for 1 d at rt. A satd $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (SiO_2; EtOAc–hexane, 1:1) afforded a colorless oil (346 mg, 92%). The analytical data were consistent with the literature data:[12] ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): $\delta = 1.45$ (s, 3H), 1.48 (s, 9H), 1.51 (s, 3H), 2.65 (dd, $J = 5.2$, 17.2 Hz, 1H), 2.95 (dd, $J = 5.6$, 14.4 Hz, 1H), 3.85–4.19 (m, 6H), 7.29–7.34 (m, 5H); IR (neat): 1783, 1697 cm^{-1}; $[\alpha]_D^{23} = -133.0$ (c 1.16, $CHCl_3$).

5.3. Asymmetric cycloaddition, followed by alkylation

5.3.1. Representative procedure for the synthesis of 13: (3*S*)-2-benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4,4-dimethylisoxazolidin-5-one 13aA. To a solution of ethyl-2,2-dibromopropanoate (312 mg, 1.2 mmol) in anhydrous THF (6 mL), cooled to −78 °C, was added dropwise a solution of *t*-BuLi (3.3 mL, 4.8 mmol, 1.47 M in pentane). The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, a solution of nitrone **7** (334 mg, 1.0 mmol) in THF (2 mL) was added to the colorless reaction mixture. After the reaction was stirred for 1 h at 0 °C, HMPA (0.52 mL, 3.0 mmol) and MeI (0.31 mL, 5 mmol) were added. The mixture was stirred for 2 h at 0 °C, and a satd $NaHCO_3$ solution (15 mL) was then added. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with H_2O and brine (20 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (SiO_2; EtOAc–hexane, 1:9) afforded a colorless oil (328 mg, 81%): ^{1}H NMR (400 MHz, DMSO, 70 °C): $\delta = 1.28$ (s, 3H), 1.29 (s, 3H), 1.38 (s, 9H), 1.44 (s, 3H), 1.58 (s, 3H), 3.50 (d, $J = 8.0$ Hz, 1H), 3.94 (d, $J = 14.8$ Hz, 1H), 3.98 (dd, $J = 7.2$, 10 Hz, 1H), 4.06 (dd, $J = 1.6$, 10 Hz, 1H), 4.37 (d, $J = 14.8$ Hz, 1H), 4.42 (m, 1H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 18.8$, 24.2, 26.9, 28.3, 28.5, 45.1, 56.2, 63.7, 74.1, 81.0, 94.8, 127.6, 128.2, 128.8, 135.8, 153.0, 178.2; IR (neat): 1772, 1698 cm^{-1}; MS (FAB): $m/z = 405$ (M$^+$+H), 91 (100%); HRMS (FAB): m/z calcd for $C_{22}H_{33}N_2O_5$ (M$^+$+H), 405.2389. Found: 405.2368. $[\alpha]_D^{25} = -111.2$ (c 0.93, $CHCl_3$).

5.3.2. (3*S*,4*R*)-2-Benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-butyl-4-methylisoxazolidin-5-one 13bA. Colorless oil; purified by preparative HPLC (EtOAc–hexane, 1:9); ^{1}H NMR (400 MHz, DMSO 80 °C, a mixture of rotomer): $\delta = 0.87$ (m, 3H × 2), 1.27, 1.30 (s, 3H × 2), 1.37, 1.39 (2s, 9H × 2), 1.45, 1.47 (s, 3H × 2), 1.58, 1.59 (s, 3H × 2), 1.27–1.82 (m, 6H × 2), 3.47, 3.58 (d, $J = 8.0$ Hz, 1H × 2), 3.84–4.05 (m, 3H × 2), 4.37 (m, 1H × 2), 4.43, 4.54 (br, 1H × 2), 7.25–7.36 (m, 5H × 2); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 13.6$, 18.9, 22.8, 26.5, 26.9, 28.1, 36.9, 48.6, 56.4, 63.8, 64.0, 69.4, 80.7, 94.4, 127.2, 127.9, 128.7, 135.7, 153.0, 177.5; IR (neat): 1770, 1697 cm^{-1}; MS (EI): $m/z = 446$ (M$^+$), 246 (100%); HRMS (EI): m/z calcd for $C_{25}H_{38}N_2O_5$, 446.2781. Found: 446.2789. $[\alpha]_D^{23} = -130.1$ (c 0.96, $CHCl_3$).

5.3.3. (3*S*,4*R*)-2-Benzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-isopropyl-4-methylisoxazolidin-5-one 13cA. Colorless oil; purified by preparative HPLC (EtOAc–hexane, 1:9); ^{1}H NMR (400 MHz, DMSO, 80 °C): $\delta = 0.97$ (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.26 (s, 3H), 1.38 (s, 9H), 1.44 (s, 3H), 1.55 (s, 3H), 1.98 (m, 1H), 3.60 (d, $J = 6.8$ Hz, 1H), 3.90 (d, $J = 9.6$ Hz, 1H), 3.99–4.08 (m, 2H), 4.29–4.35 (m, 2H), 7.24–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 17.5$, 17.9, 27.1, 28.3, 34.2, 51.3, 56.8, 64.7, 69.3, 80.7, 94.7, 127.5, 128.2, 129.0, 136.0, 153.2, 178.0; IR (neat): 1765, 1697 cm^{-1}; MS (EI): $m/z = 432$ (M^+), 92 (100%); HRMS (EI): m/z calcd for $C_{24}H_{36}N_2O_5$, 432.2624. Found: 432.2609. $[\alpha]_D^{24} = -122.0$ (c 1.06, $CHCl_3$).

5.3.4. (3*S*,4*R*)-2,4-Dibenzyl-3-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-methylisoxazolidin-5-one 13aB. Colorless needles; mp 131.9–132.2 °C (Et_2O–hexane); ^{1}H NMR (400 MHz, DMSO, 70 °C): $\delta = 1.32$ (s, 12H), 1.47 (s, 3H), 1.48 (s, 3H), 2.90 (d, $J = 14.0$ Hz, 1H), 3.13 (d, $J = 14.0$ Hz, 1H), 3.36 (br s, 1H), 3.38 (d, $J = 9.2$ Hz, 1H), 3.81 (br s, 1H), 3.95 (m, 1H), 4.03 (d, $J = 14.4$ Hz, 1H), 4.42 (br s, 1H), 7.21–7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.5$, 24.8, 27.6, 28.2, 44.3, 50.6, 57.8, 64.3, 65.0, 68.3, 80.9, 94.4, 126.6, 127.3, 127.9, 128.4, 130.5, 135.6, 135.9, 153.1, 177.6, 177.7; IR ($CHCl_3$): 1762, 1691 cm^{-1}; MS (EI): $m/z = 480$ (M^+), 57 (100%). Anal. Calcd for $C_{28}H_{36}N_2O_5$: C, 69.98; H, 7.55; N, 5.83. Found: C, 69.74; H, 7.56; N, 5.80. $[\alpha]_D^{24} = -212.0$ (c 1.13, $CHCl_3$). Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-273642. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

5.4. Conversion into β-lactams

5.4.1. Representative procedure for the synthesis of 17: (3*R*,4*S*)-4-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-methylazetidin-2-one 17a. The isoxazolidinone **12aA** (128 mg, 0.33 mmol) was added to a suspension of 10% Pd/C (25 mg, 20% w/w) in methanol under H_2 at 4.0 atm, and the mixture stirred at room temperature for 2 h. The solution was filtered, and the solvents removed in vacuo to afford the β-amino acid **14a** (100 mg, >99%). To a solution of β-amino acid **14a** (100 mg, 0.33 mmol) in $CHCl_3$ (1.5 mL) and H_2O (0.3 mL), were added Bu_4NHSO_4 (16.8 mg, 0.04 mmol) and $KHCO_3$ (132.4 mg, 1.32 mmol). MsCl (0.05 mL, 0.66 mmol) was added, and the mixture stirred vigorously at room temperature for 0.5 h. The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic phase washed with brine (10 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (SiO_2; EtOAc–hexane, 1:1) afforded **17a** (86.6 mg, 92%): Colorless prisms; mp 102.2–102.7 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (d, $J = 7.6$ Hz, 3H), 1.48 (s, 9H), 1.54 (s, 6H), 2.98 (br, 1H), 3.44 (br, 1H), 3.79 (br, 1H), 4.04 (br, 2H), 6.13 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.1$, 24.4, 27.2, 28.3, 48.3, 58.5, 59.5, 64.4, 80.9, 94.3, 153.1, 170.6; IR ($CHCl_3$): 1759, 1683 cm^{-1}; MS (EI): $m/z = 284$ (M^+), 170 (100%). Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85. Found: C, 58.89; H, 8.35; N, 9.84. $[\alpha]_D^{25} = -18.2$ (c 1.02, $CHCl_3$).

5.4.2. (3*R*,4*S*)-4-((*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-butylazetidin-2-one 17b. Colorless oil; purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 6.8$ Hz, 3H), 1.48 (s, 9H), 1.57 (s, 3H), 1.63 (s, 3H), 1.75 (m, 1H), 1.30–1.63 (m, 5H), 2.93 (br, 1H), 3.52 (br, 1H), 3.81 (br, 1H), 4.00 (m, 2H), 6.15 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$, 22.6, 24.2, 27.1, 28.3 (×4), 29.3, 53.6, 56.6, 59.5, 64.4, 80.9, 94.4, 153.2, 170.4; IR (neat): 1757, 1695 cm^{-1}; MS (FAB): $m/z = 327$ (M^++H), 154 (100%); HRMS (FAB): m/z calcd for $C_{17}H_{31}N_2O_4$ (M^++H), 327.2284. Found: 327.2290. $[\alpha]_D^{27} = -22.3$ (c 1.10, $CHCl_3$).

5.4.3. (3*R*,4*S*)-4-((*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-isopropylazetidin-2-one 17c. Colorless oil; purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.02$ (d, $J = 6.4$ Hz, 3H), 1.08 (d, $J = 7.2$ Hz, 3H), 1.48 (s, 12H), 1.58 (s, 3H), 1.98 (m, 1H), 2.76 (br, 1H), 3.59 (m, 1H), 3.86 (dd, $J = 9.6$, 8.4 Hz, 1H), 3.99 (dd, $J = 9.6$, 6.4 Hz, 1H), 4.06 (m, 1H), 5.90–6.20 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 20.8, 24.3, 27.2, 27.8, 28.4, 54.3, 59.6, 60.0, 64.3, 80.8, 94.3, 153.0, 169.7; IR (neat): 1757, 1697 cm^{-1}; MS (EI): $m/z = 312$ (M^+), 113 (100%); HRMS (EI): m/z calcd for $C_{16}H_{28}N_2O_4$, 312.2049. Found: 312.2029. $[\alpha]_D^{27} = -28.3$ (c 1.17, $CHCl_3$).

5.4.4. (3*R*,4*S*)-4-((*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-phenylazetidin-2-one 17d. Colorless oil; purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.49$ (s, 12H), 1.53 (s, 3H), 3.87–4.40 (m, 5H), 6.47 (br, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.5$, 27.2, 28.4, 58.5, 58.9, 59.6, 64.5, 81.0, 94.5, 127.3, 127.4, 128.7, 134.3, 153.0, 167.7; IR (neat): 1763, 1689 cm^{-1}; MS (FAB): $m/z = 347$ (M^++H), 369 (100%, M^++Na); HRMS (FAB): m/z calcd for $C_{19}H_{26}N_2O_4Na$ (M^++Na), 369.1790. Found: 369.1766. $[\alpha]_D^{26} = -24.7$ (c 1.60, $CHCl_3$).

5.4.5. (3*R*,4*S*)-4-((*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-butyl-3-methylazetidin-2-one 17e. Colorless oil; purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.4$ Hz, 3H), 1.18 (s, 3H), 1.25–1.63 (m, 21H), 3.42 (d, $J = 9.6$ Hz, 1H), 3.65 (br d, $J = 8.8$ Hz, 1H), 4.07 (m, 2H), 6.38 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 15.8, 23.1, 24.5, 26.7, 27.7, 28.4, 36.0, 57.8, 59.2, 61.3, 65.3, 80.9, 94.0, 153.3, 172.8; IR (neat): 1762, 1698 cm^{-1}; MS (APCI$^+$): $m/z = 341$ (M^++H); HRMS (APCI$^+$): m/z calcd for $C_{18}H_{33}N_2O_4$(M^++H), 341.2440. Found: 341.2426. $[\alpha]_D^{26} = -20.2$ (c 1.22, $CHCl_3$).

5.4.6. (3*R*,4*S*)-4-((*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-isopropyl-3-methylazetidin-2-one 17f. Colorless oil; purified by column chromatography (EtOAc–hexane, 1:1) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.15 (s, 3H), 1.48 (s, 15H), 1.89 (m, 1H), 3.41 (d, $J = 8.8$ Hz, 1H), 3.57 (d, $J = 8.8$ Hz, 1H), 4.00 (m, 1H), 4.10 (m, 1H), 6.42 (br, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): $\delta = 12.5$, 17.7, 18.3, 24.4, 27.8, 28.5, 32.5, 59.3, 59.5, 61.7, 65.4, 81.0, 94.0, 153.3, 172.8; IR (neat): 1762, 1698 cm^{-1}; MS (APCI$^+$): $m/z = 327$ (M+H); HRMS (APCI$^+$): m/z calcd for $C_{17}H_{31}N_2O_4$ (M^++H), 327.2284. Found: 327.2278. $[\alpha]_D^{26} = -21.0$ (*c* 0.91, $CHCl_3$).

5.5. Conversion to *N*-benzyl-β-lactams

5.5.1. Representative procedure for the synthesis of 18: (3*R*,4*S*)-1-benzyl-4-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-methylazetidin-2-one 18a. To a solution of β-lactam **17a** (25 mg, 0.08 mmol) in CH_2Cl_2 (1.5 mL) and 30% aq NaOH (1.5 mL), was added Bu_4NHSO_4 (16.8 mg, 0.04 mmol). Benzyl bromide (0.01 mL, 0.13 mmol) was added and the mixture stirred vigorously at room temperature for 2 h. H_2O was added to the resulting mixture, which was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (SiO_2; EtOAc–hexane, 3:7) afforded **18a** (32.4 mg, 98%): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$, 1.26 (s, 3H × 2), 1.36, 1.49 (s, 9H × 2), 1.41, 1.42 (s, 3H × 2), 1.45, 1.52 (s, 3H × 2), 3.13, 3.23 (m, 1H × 2), 3.41, 3.52 (br s, 1H × 2), 3.55–3.76 (m, 2H × 2), 3.83, 4.02 (br s, 1H × 2), 4.18 (d, $J = 14.8$ Hz, 1H), 4.37 (s, 2H), 4.50 (d, $J = 14.8$ Hz, 1H), 7.23–7.53 (m, 5H × 2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.0$, 22.5, 24.0, 26.6, 27.3, 28.3, 45.1, 45.2, 46.3, 46.5, 55.9, 56.9, 59.4, 60.0, 62.3, 62.7, 80.2, 80.7, 94.0, 94.4, 127.6, 127.8, 128.1, 128.3, 128.7, 128.8, 135.8, 136.4, 151.4, 152.5, 171.1; IR (neat): 1753, 1698 cm^{-1}; MS (FAB): $m/z = 375$ (M+H), 57 (100%); HRMS (FAB): m/z calcd for $C_{21}H_{31}N_2O_4$ (M^++H), 375.2284. Found: 375.2271. $[\alpha]_D^{26} = +8.7$ (*c* 1.39, $CHCl_3$).

5.5.2. (3*R*,4*S*)-1-Benzyl-3-butyl-4-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-azetidin-2-one 18b. Colorless oil; purified by column chromatography (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.8$ Hz, 3H × 2), 1.25–1.71 (m, 21H × 2), 3.06, 3.15 (m, 1H × 2), 3.51 (br s, 1H × 2), 3.66 (m, 1H × 2, 1H), 3.79 (br s, 1H), 3.81, 4.01 (br s, 1H × 2), 4.12 (d, $J = 15.2$ Hz, 1H), 4.33 (d, $J = 16$ Hz, 1H), 4.38 (d, $J = 16$ Hz, 1H), 4.52 (d, $J = 15.2$ Hz, 1H), 7.25–7.37 (m, 5H × 2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 23.8, 22.3, 22.7, 26.4, 27.1, 28.3, 28.4, 29.5, 45.0, 45.1, 51.5, 51.7, 55.9, 56.9, 57.2, 58.2, 62.2, 62.5, 80.2, 80.7, 94.3, 94.7, 127.6, 127.9, 128.3, 128.4, 128.8, 128.9, 135.8, 136.5, 151.6, 152.8, 170.9. IR (neat): 1751, 1698 cm^{-1}; MS (EI): $m/z = 416$ (M^+), 188 (100%); HRMS (EI): m/z calcd for $C_{24}H_{36}N_2O_4$, 416.2675. Found: 416.2682. $[\alpha]_D^{27} = +1.8$ (*c* 0.92, $CHCl_3$).

5.5.3. (3*R*,4*S*)-1-Benzyl-4-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-isopropylazetidin-2-one 18c. Colorless oil; purified by column chromatography (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (d, $J = 6.6$ Hz, 3H × 2), 1.04 (d, $J = 6.6$ Hz, 3H × 2), 1.33–1.56 (m, 15H × 2), 1.76, 1.90 (m, 1H × 2), 2.88, 2.98 (br d, $J = 7.3$ Hz, 1H × 2), 3.49 (m, 1H × 2), 3.61–3.85 (m, 2H × 2, 1H × 2, 1H), 4.03 (br s, 1H), 4.05 (d, $J = 15.3$ Hz, 1H), 4.35 (s, 2H), 4.57 (d, $J = 15.3$ Hz, 1H), 7.26–7.34 (m, 5H × 2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 20.2, 20.9, 21.1, 22.4, 23.8, 26.5, 27.2, 28.2, 28.4, 44.8, 45.1, 54.8, 56.9, 55.92, 55.99, 57.7, 58.1, 62.1, 62.4, 80.2, 80.7, 94.9, 94.8, 127.5, 127.7, 128.2, 128.4, 128.6, 128.7, 135.6, 136.4, 151.6, 152.7, 169.9, 170.1; IR (neat): 1747, 1695 cm^{-1}; MS (EI): $m/z = 402$ (M^+), 174 (100%); HRMS (EI): m/z calcd for $C_{23}H_{34}N_2O_4$, 402.2519. Found: 402.2539. $[\alpha]_D^{27} = -12.1$ (*c* 0.84, $CHCl_3$).

5.5.4. (3*R*,4*S*)-1-Benzyl-4-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-phenylazetidin-2-one 18d. Colorless oil; purified by column chromatography (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.30$ (s, 3H × 2), 1.41–1.51 (m, 12H × 2), 3.57, 3.72 (m, 1H × 2), 3.72, 4.01 (br, 1H × 2), 3.92 (br d, $J = 10.0$Hz, 1H × 2), 4.13 (br d, $J = 7.6$ Hz, 1H × 2), 4.26 (d, $J = 14.8$ Hz, 1H), 4.34–4.49 (m, 1H × 2), 4.42 (d, $J = 15.6$ Hz, 1H), 4.48 (d, $J = 15.6$ Hz, 1H), 4.56 (d, $J = 14.8$ Hz, 1H), 7.23–7.41 (m, 10H × 2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.6$, 24.0, 26.7, 27.4, 28.4, 45.4, 45.5, 55.9, 56.0, 56.3, 57.0, 58.9, 59.5, 62.2, 62.5, 80.4, 80.8, 94.3, 94.8, 127.0, 127.1, 127.2, 127.7, 127.9, 128.1, 128.2, 128.4, 128.50, 128.57, 128.7, 128.8, 134.6, 135.4, 136.2, 151.3, 152.5, 168.4; IR (neat): 1756, 1698 cm^{-1}; MS (FAB): $m/z = 437$ (M+H), 91 (100%); HRMS (FAB): m/z calcd for $C_{26}H_{33}N_2O_4$ (M^++H), 437.2440. Found: 437.2458. $[\alpha]_D^{27} = +38.1$ (*c* 0.96, $CHCl_3$).

5.5.5. (3*R*,4*S*)-1-Benzyl-4-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-butyl-3-methylazetidin-2-one 18e. Colorless oil; purified by column chromatography (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.4$ Hz, 3H), 1.18–1.28 (m, 12H), 1.50–1.64 (m, 12H), 3.20 and 3.22 (br, 1H), 3.49 and 3.52 (br, 1H), 3.67 (d, $J = 14.2$ Hz, 1H), 3.91 (m, 1H), 4.23 and 4.33 (br, 1H), 4.97 (d, $J = 14.2$ Hz, 1H), 7.21–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$, 15.7, 23.2, 24.7, 26.8, 27.8, 28.6, 36.1, 44.5, 56.1, 58.1, 61.1, 65.5, 80.9, 94.3, 127.4, 128.3, 128.6, 136.1, 153.1, 173.3; IR ($CHCl_3$): 1750, 1696 cm^{-1}; MS (APCI$^+$): $m/z = 431$ (M^++H); HRMS (APCI$^+$): m/z calcd for $C_{25}H_{39}N_2O_4$ (M^++H), 431.2910. Found: 431.2896. $[\alpha]_D^{28} = +0.2$ (*c* 0.92, $CHCl_3$).

5.5.6. (3*R*,4*S*)-1-Benzyl-4-((*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-3-methyl-3-isopropylazetidin-2-one 18f. Colorless prisms; mp 109–110 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 1.14 (s, 3H), 1.30 (br, 3H), 1.51 (s, 3H), 1.57 (s, 9H), 1.80 (m, 1H), 3.24, 3.26 (br s, 1H), 3.59, 3.62 (br s, 1H), 3.85 (m, 2H), 4.34 (br s, 1H), 4.95 (d, $J = 14.8$ Hz, 1H), 7.22–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.9$, 17.9, 18.6, 24.8, 27.9, 28.6, 33.0, 44.4, 58.2, 59.9, 64.9, 65.5, 80.9, 94.3, 127.4, 128.3, 128.7, 136.2, 153.2, 173.1; IR ($CHCl_3$): 1734, 1687 cm^{-1}; MS (APCI$^+$): $m/z = 417$ (M^++H); HRMS (APCI$^+$): m/z calcd for

$C_{24}H_{37}N_2O_4$ (M^++H), 417.2753. Found: 417.2764. $[\alpha]_D^{28} = -14.3$ (*c* 0.54, $CHCl_3$).

5.6. Conversion into γ-lactams

5.6.1. Representative procedure for the synthesis of 23: (3*S*,4*S*,5*R*)-4-benzylamino-5-(*tert*-butyldiphenylsiloxymethyl)-3-methylpyrrolidin-2-one 23a. A solution of the β-lactam **18a** (20 mg, 0.05 mmol) in 25% HCl–EtOH (2 mL) was refluxed for 6 h. After removal of the solvent under reduced pressure, the residue was diluted with H_2O and EtOAc. The solution was cooled to 0 °C, and Et_3N was added until pH 9. The resulting mixture was saturated with NaCl and extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2, and imidazole (5 mg, 0.07 mmol) and a catalytic amount of 4-DMAP added. TBDPSCl (0.01 mL, 0.06 mmol) was added to the resulting mixture, which was stirred at room temperature for 4 h. Water was added, and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (SiO_2; EtOAc–hexane, 1:1) afforded **23a** (6.5 mg, 26%); Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (s, 9H), 1.16 (d, $J = 7.2$ Hz, 3H), 1.60 (br, 1H), 2.31 (dq, $J = 7.2$, 10.0 Hz, 1H), 3.13 (dd, $J = 7.6$, 10.0 Hz, 1H), 3.56 (m, 1H), 3.63 (d, $J = 12.8$ Hz, 1H), 3.67 (d, $J = 12.8$ Hz, 1H), 3.61–3.73 (m, 2H), 5.65 (br, 1H), 7.11–7.37 (m, 10H), 7.53–7.64 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.6$, 19.2, 26.9, 42.2, 52.6, 56.1, 63.2, 63.7, 127.0, 127.7, 127.8, 128.3, 129.7, 129.8, 132.4, 132.6, 135.3, 135.4, 139.6, 177.9; IR (neat): 1698 cm^{-1}; MS (EI): $m/z = 472$ (M^+), 415 (100%); HRMS (EI): m/z calcd for $C_{29}H_{36}N_2O_2Si$, 472.2546. Found: 472.2524. $[\alpha]_D^{27} = -48.5$ (*c* 0.83, $CHCl_3$).

5.6.2. (3*S*,4*S*,5*R*)-4-(Benzylamino)-3-butyl-5-(*tert*-butyldiphenylsiloxymethyl)pyrrolidin-2-one 23b. Pale yellow oil: purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.8$ Hz, 3H), 1.03 (s, 9H), 1.25–1.71 (m, 6H), 2.33 (m, 1H), 3.29 (m, 1H), 3.64–3.81 (m, 5H), 5.71 (br s, 1H), 7.16–7.44 (m, 6H), 7.61–7.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 19.2, 23.0, 26.9, 29.0, 29.1, 46.9, 52.5, 56.1, 60.4, 63.9, 127.0, 127.5, 127.7, 127.8, 128.3, 129.4, 129.7, 129.8, 132.5, 132.6, 134.6, 135.3, 135.4, 177.6; IR (neat): 1698 cm^{-1}; MS (APCI$^+$): $m/z = 515$ (M+H); HRMS (APCI$^+$): m/z calcd for $C_{32}H_{43}N_2O_2Si$ (M^++H), 515.3094. Found: 515.3113. $[\alpha]_D^{27} = -45.2$ (*c* 0.53, $CHCl_3$).

5.6.3. (3*S*,4*S*,5*R*)-4-(Benzylamino)-5-(*tert*-butyldiphenylsiloxymethyl)-3-isopropylpyrrolidin-2-one 23c. Yellow oil: purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.04 (s, 9H), 2.17 (m, 1H), 2.27 (dd, $J = 3.8$, 8.5 Hz, 1H), 3.37 (dd, $J = 7.8$, 8.5 Hz, 1H), 3.59 (d, $J = 13.2$ Hz, 1H), 3.64 (d, $J = 13.2$ Hz, 1H), 3.64 (m, 1H), 3.75 (m, 2H), 5.71 (br s, 1H), 7.13–7.15 (m, 2H), 7.22–7.47 (m, 9H), 7.60–7.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.2$, 19.3, 20.0, 26.9, 27.5, 52.5, 52.8, 56.4, 57.0, 64.2, 127.0, 127.7, 127.9, 128.2, 129.7, 129.8, 132.6, 132.7, 135.3, 135.4, 139.4, 176.9; IR (neat): 1698 cm^{-1}; MS (APCI$^+$): $m/z = 501$ (M^++H); HRMS (APCI$^+$): m/z calcd for $C_{31}H_{41}N_2O_2Si$ (M+H), 501.2937. Found: 501.2943. $[\alpha]_D^{28} = -45.2$ (*c* 0.28, $CHCl_3$).

5.6.4. (3*S*,4*S*,5*R*)-4-(Benzylamino)-5-(*tert*-butyldiphenylsiloxymethyl)-3-phenylpyrrolidin-2-one 23d. Orange oil: purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 0.85$ (s, 9H), 2.86 (br, 1H), 3.00 (d, $J = 12.8$ Hz, 1H), 3.06 (d, $J = 12.8$ Hz, 1H), 3.16 (dd, $J = 7.6$, 10.4 Hz, 1H), 3.28 (dd, $J = 2.8$, 10.8 Hz, 1H), 3.40 (d, $J = 10.4$ Hz, 1H), 3.49 (dd, $J = 4.8$, 10.8 Hz, 1H), 5.78 (br s, 1H), 6.64–6.66 (m, 2H), 6.74–6.99 (m, 9H), 7.46–7.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.2$, 27.0, 52.2, 54.6, 56.3, 63.6, 63.8, 126.9, 127.2, 127.73, 127.77, 128.2, 128.5, 128.7, 129.7, 129.8, 132.5, 132.6, 135.4, 135.5, 137.5, 139.2, 175.7; IR (neat): 1701 cm^{-1}; MS (APCI$^+$): $m/z = 535$ (M+H); HRMS (APCI$^+$): m/z calcd for $C_{34}H_{39}N_2O_2Si$ (M+H), 535.2781. Found: 535.2808. $[\alpha]_D^{27} = -55.7$ (*c* 0.19, $CHCl_3$).

5.6.5. (3*R*,4*S*,5*R*)-4-(Benzylamino)-5-(hydoxymethyl)-3-isopropyl-3-methylpyrrolidin-2-one 20f. Colorless oil: purified by column chromatography (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (d, $J = 6.8$ Hz, 3H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.20 (s, 3H), 1.64 (br, 2H), 2.03 (m, 1H), 3.36 (d, $J = 6.4$ Hz, 1H), 3.76 (ddd, $J = 6.4$, 6.4, 7.2 Hz, 1H), 3.83 (d, $J = 12.8$ Hz, 1H), 3.84 (dd, $J = 6.4$, 11.6 Hz, 1H), 3.90 (d, $J = 12.8$ Hz, 1H), 3.91 (dd, $J = 7.2$, 11.6 Hz, 1H), 5.82 (br, 1H), 7.29–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.00$, 19.07, 19.8, 29.2, 49.1, 54.7, 54.9, 62.7, 67.6, 127.5, 128.0, 128.6, 138.6, 180.0; IR (neat): 3329, 1679 cm^{-1}; MS (APCI$^+$): $m/z = 277$ (M^++H); HRMS (APCI$^+$): m/z calcd for $C_{16}H_{25}N_2O_2$ (M^++H), 277.1916. Found: 277.1940. $[\alpha]_D^{26} = -59.9$ (*c* 0.23, $CHCl_3$).

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