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Asymmetric synthesis of 4-formyl-1-(ω-haloalkyl)-β-lactams and their transformation to functionalized piperazines and 1,4-diazepanes

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ABSTRACT

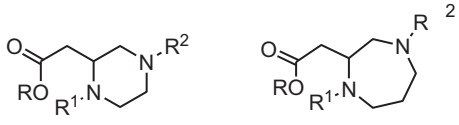
Chiral piperazine and 1,4-diazepane annulated β-lactams, prepared from the corresponding (3*R*,4*S*)-4-imidoyl-1-(ω-haloalkyl)azetidin-2-ones through reduction with sodium borohydride in ethanol, were transformed into novel methyl (*R*)-alkoxy-[(*S*)-piperazin-2-yl]acetates and methyl (*R*)-alkoxy-[(*S*)-1,4-diazepan-2-yl]acetates upon treatment with hydrogen chloride in methanol. On the other hand, bromination of (3*R*,4*R*)-1-allyl-4-formyl-β-lactams and (3*R*,4*S*)-1-allyl-4-imidoyl-β-lactams in dichloromethane, followed by sodium borohydride reduction of the resulting dibrominated azetidin-2-ones in ethanol, did not afford the envisaged bicyclic β-lactams but unexpectedly furnished (3*R*,4*S*)-1-(2-bromo-2-propenyl)azetidin-2-ones instead.

1. Introduction

Piperazine and 1,4-diazepane chemistry is of significant pharmaceutical importance because of the occurrence of these scaffolds in a large number of biologically active compounds useful in different therapeutical areas.[1] Hence, the search for new, functionalized piperazines and 1,4-diazepanes remains a relevant issue in medicinal chemistry. Furthermore, as β-amino acids and their derivatives undergo little or no degradation by peptidases and thus exhibit a potential biological activity,[2] the preparation of optically active piperazines and 1,4-diazepanes **1** and **2** comprises a valuable entry toward new drug compounds. In that respect, the preparation of a chiral (piperazin-2-yl)acetate as an intermediate in the synthesis of a renin inhibitor via a diastereoselective Dieckmann cyclization has been described recently.[3]

From a synthetic point of view, the use of chiral piperazine and 1,4-diazepane annulated β-lactams could be useful in the synthesis of the target compounds **1** and **2** as azetidin-2-ones are known to be excellent building blocks (cfr. 'β-lactam synthon method').[4] However, only one enantioselective approach to chiral (piperazin-2-yl)acetates, starting from fused oxopiperazino-β-lactams, is available in the literature to date.[5]

In this paper, an efficient and straightforward approach toward chiral methyl (piperazin-2-yl)acetates and methyl (1,4-diazepan-2-yl)acetates is disclosed starting from 1,4-diazabicyclo[4.2.0]octan-8-ones and 1,5-diazabicyclo[5.2.0]nonan-9-ones via ring opening using a saturated solution of HCl in MeOH. Furthermore, an attempt to extend this approach toward the use of 1-allyl-β-lactams as starting compounds is described, albeit resulting in the unexpected synthesis of 1-(2-bromo-2-propenyl)-β-lactams upon bromination and subsequent $NaBH_4$ reduction.



1 **2**

2. Results and discussion

The synthesis of chiral 4-formyl-1-(ω-haloalkyl)-β-lactams **5a**–**d** was performed by means of a slightly modified four-step literature procedure.[6,7] (*R*)-Glyceraldehyde acetonide **3** was condensed with 2-chloroethyl- or 3-bromopropylamine (in situ prepared from the corresponding hydrohalide salts using 3 equiv of Et_3N) in dichloromethane in the presence of $MgSO_4$, and the

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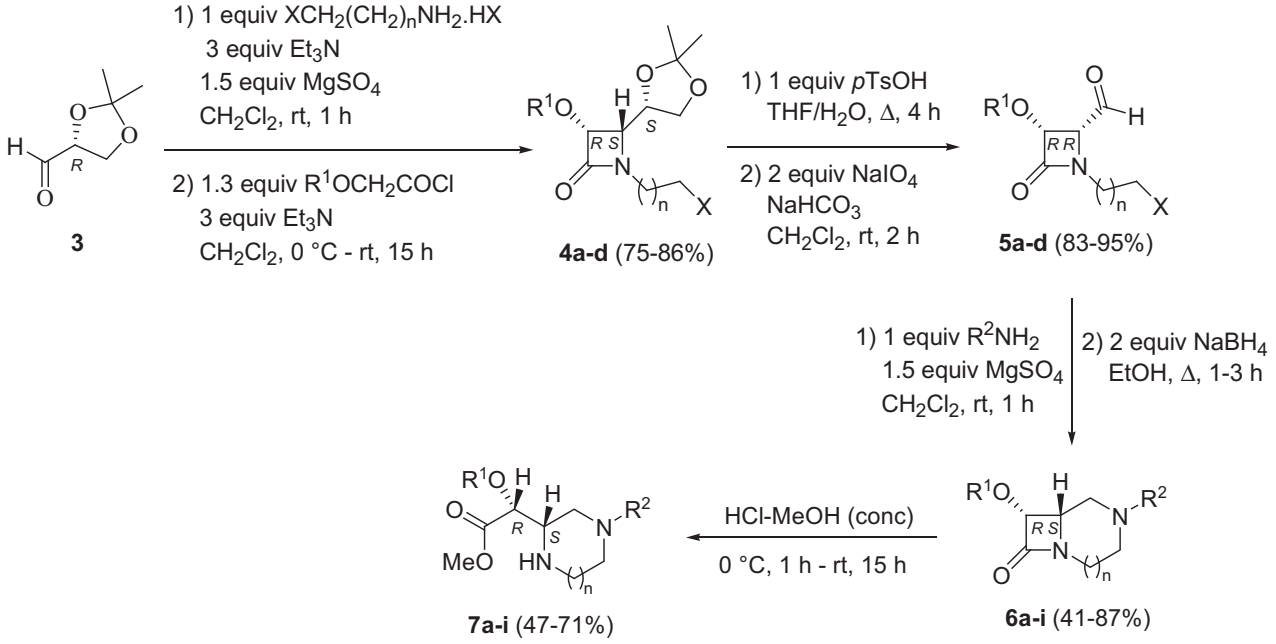
resulting imines were used as substrates for a Staudinger reaction using benzyloxy- or methoxyacetyl chloride in dichloromethane to synthesize β-lactams **4a**–**d** in a highly stereoselective way (Scheme 1, Table 1). The Staudinger reaction, in which an imine and a ketene undergo a [2+2]-cyclocondensation reaction, indeed comprises a very reliable and robust method for the preparation of β-lactam derivatives.[8] The latter azetidin-2-ones **4a**–**d** could be easily converted into the premised (3*R*,4*R*)-4-formyl-β-lactams **5a**–**d** by consecutive hydrolysis using 4-toluenesulfonic acid in THF and oxidation of the resulting diol by sodium periodate in a two-phase system of aqueous $NaHCO_3$ and CH_2Cl_2 at room temperature for 2 h (Scheme 1, Table 1).[7] 4-Formylazetidin-2-ones have proven to be valuable synthons in organic chemistry, as they, for example, have been used for the asymmetric synthesis of polycyclic β-lactams, indolizidine, and quinolizidine derivatives,[9] and biologically active compounds like biotin, cisapride, and sphingosines.[10]

Because of the importance of chirality in medicinal chemistry, and since asymmetric syntheses of optically active 2-substituted piperazines in general[11] and chiral alkyl (piperazin-2-yl)acetates in particular[5] are relatively scarce, this approach comprises a convenient entry toward the latter class of compounds. Moreover, through variation of the length of the 1-haloalkyl moiety in azetidin-2-ones **5a**–**d**, the preparation of chiral methyl [(*S*)-1,4-diazepan-2-yl]acetates as the higher homologues has been made possible as well.

In order to extend the scope of this study, the use of (3*R*,4*R*)-1-allyl-4-formyl-β-lactams **5e**–**g** as starting compounds for the synthesis of oxa- and azaheterocyclic annulated β-lactams containing an additional functionality (i.e., the presence of a bromine atom), was then evaluated. Applying the same reaction protocol as described above, the synthesis of chiral 1-allyl-4-formylazetidin-2-



Scheme 1.

Table 1
Synthesis of azetidin-2-ones **4a**–**d** and 4-formylazetidin-2-ones **5a**–**d**

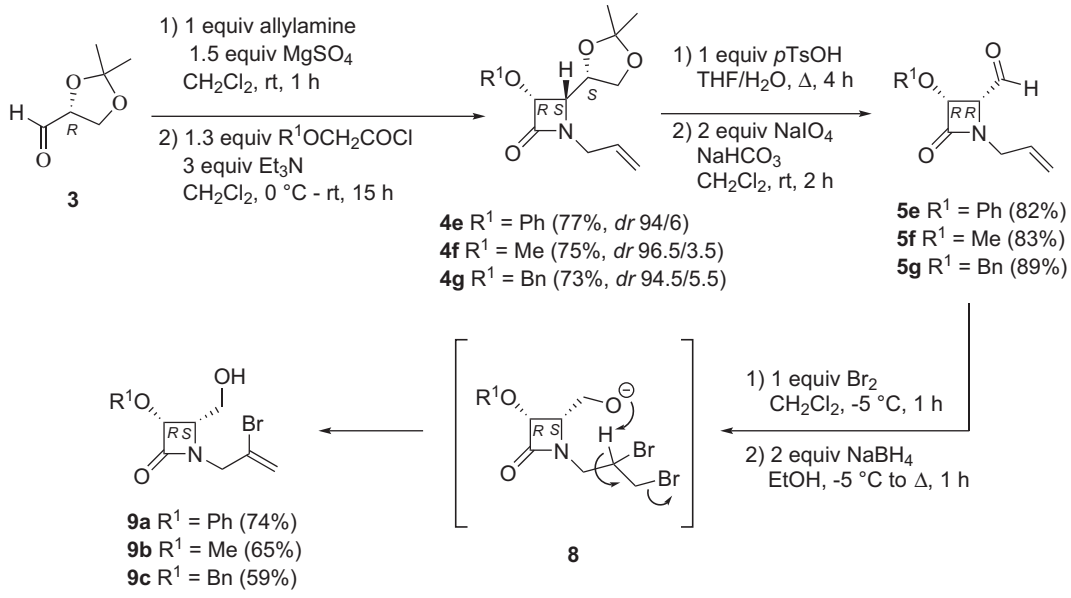
Entry	X	*n*	R^1	Compound (% yield)	*dr*	Compound (% yield)
1	Cl	1	Me	**4a** (81%)	91.5/8.5	**5a** (83%)
2	Cl	1	Bn	**4b** (86%)	93.5/6.5	**5b** (94%)
3	Br	2	Me	**4c** (75%)	95.5/4.5	**5c** (94%)
4	Br	2	Bn	**4d** (77%)	94/6	**5d** (95%)

Imination of 4-formyl-1-(2- and 3-haloalkyl)azetidin-2-ones **5a**–**d** upon treatment with 1 equiv of a primary amine in CH_2Cl_2 in the presence of $MgSO_4$ and subsequent reduction with $NaBH_4$ in EtOH under reflux for 1–3 h afforded bicyclic β-lactams **6**,[7] which were then treated with a saturated solution of hydrogen chloride gas in MeOH for 15 h at room temperature to afford novel methyl (*R*)-[(*S*)-piperazin-2-yl]acetates **7a**–**d** and methyl (*R*)-[(*S*)-1,4-diazepan-2-yl]acetates **7e**–**i** in good yields through acid-promoted methanolysis of the β-lactam ring (Scheme 1, Table 2). It should be noted that the yields (47–71%) are those obtained after column chromatography on silica gel. When shorter reaction times were applied, significant amounts of starting compound **6** were recovered, especially for the 1,4-diazepane annulated β-lactams, probably due to the lower ring strain compared with their six-membered analogues.

Table 2
Synthesis of methyl (*R*)-[(*S*)-piperazin-2-yl]acetates **7a**–**d** and methyl (*R*)-[(*S*)-1,4-diazepan-2-yl]acetates **7e**–**i**

Entry	X	*n*	R^1	R^2	Compound (% yield)
1	Cl	1	Me	Allyl	**7a** (66%)
2	Cl	1	Me	Bn	**7b** (70%)
3	Cl	1	Me	*t*-Bu	**7c** (63%)
4	Cl	1	Bn	*i*-Pr	**7d** (71%)
5	Br	2	Me	Bn	**7e** (68%)
6	Br	2	Me	Allyl	**7f** (69%)
7	Br	2	Me	*i*-Pr	**7g** (47%)
8	Br	2	Bn	*t*-Bu	**7h** (64%)
9	Br	2	Bn	Allyl	**7i** (63%)

ones **5e**–**g** was achieved starting from allylamine, which, after condensation with (*R*)-glyceraldehyde acetonide **3** in the presence of $MgSO_4$ and subsequent Staudinger reaction using three different acetyl chlorides, afforded β-lactams **4e**–**g** in high diastereomeric ratios (Scheme 2). Consecutive hydrolysis using 4-toluenesulfonic acid and oxidation by sodium periodate then gave rise to 4-formylazetidin-2-ones **5e**–**g**, from which the spectral data were in full correspondence with those reported in the literature (Scheme 2).[6]



Scheme 2.

In contrast to 4-formyl-1-(2- and 3-haloalkyl)-azetidin-2-ones **5a**–**d**, which selectively allowed the design of bicyclic β-lactams via an intramolecular nucleophilic substitution reaction,[6] the latter azetidin-2-ones **5e**–**g** could not be converted into morpholine and piperazine annulated β-lactams.

First, (3*R*,4*R*)-1-allyl-4-formyl-β-lactams **5e**–**g** were treated with 1 equiv of bromine in dichloromethane for 1 h at −5 °C (Scheme 2). As the resulting 1-(2,3-dibromopropyl)azetidin-2-ones were expected to be fairly unstable at room temperature, the bromination step was immediately followed by addition of ethanol and 2 equiv of $NaBH_4$ at −5 °C. Unfortunately, no bicyclic β-lactams were observed, but 1-(2-bromo-2-propenyl)azetidin-2-ones **9a**–**c** were formed instead. This reaction probably proceeds through reduction of the aldehyde function resulting in the formation of alkoxide anions **8**, which apparently do not give rise to a 6- or 7-*exo*-*tet*-cyclization as they induce dehydrobromination through deprotonation of the C2 hydrogen atom of the 2,3-dibromopropyl moiety, affording vinyl bromides **9a**–**c** in good yields (Scheme 2). Alternatively, sodium ethoxide can also account for the latter deprotonation.

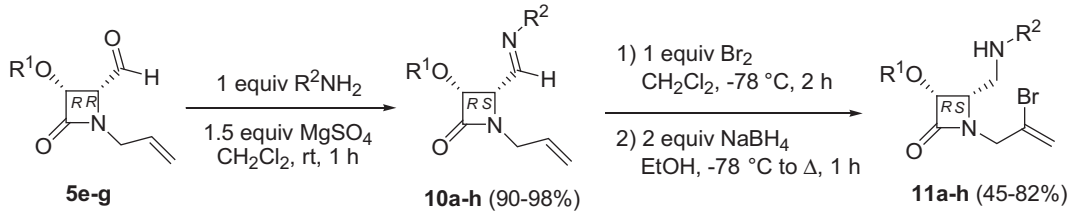
As the synthesis of oxaheterocyclic annulated β-lactams starting from 1-allylazetidin-2-ones **5e**–**g** was unsuccessful, the preparation of their nitrogen analogues was attempted. In that respect, 4-formyl-β-lactams **5e**–**g** were condensed with 1 equiv of different primary amines in dichloromethane in the presence of $MgSO_4$, furnishing 4-imidoyl-β-lactams **10** in excellent yields after 1 h at room temperature (Scheme 3, Table 3). When the aforementioned reaction procedure was applied to 4-imidoyl-β-lactams **10**, i.e., treatment with 1 equiv of bromine in dichloromethane at −5 °C and subsequent reduction with 2 equiv of $NaBH_4$ in EtOH, a complex reaction mixture was obtained, probably because of the instability of the obtained dibromoimines at this temperature. On the other hand, bromination at −78 °C followed by reduction with $NaBH_4$ in EtOH afforded single reaction products, but spectral analysis revealed that again 1-(2-bromo-2-propenyl)azetidin-2-ones **11a**–**h** were formed (Scheme 3, Table 3). A solvent switch from EtOH to MeOH did not result in piperazine and morpholine annulated β-lactams either, but afforded a more complex reaction mixture, still with 1-(2-bromo-2-propenyl)azetidin-2-ones as the main reaction products.

Table 3
Synthesis of (3*R*,4*S*)-1-allyl-4-imidoyl-β-lactams **10** and (3*R*,4*S*)-4-(aminomethyl)-1-(2-bromo-2-propenyl)azetidin-2-ones **11**

Entry	R^1	R^2	Compound (% yield)	Compound (% yield)
1	Ph	*t*-Bu	**10a** (90%)	**11a** (71%)
2	Ph	*i*-Pr	**10b** (95%)	**11b** (62%)
3	Ph	Bn	**10c** (97%)	**11c** (48%)
4	Me	*t*-Bu	**10d** (96%)	**11d** (64%)
5	Me	*i*-Pr	**10e** (98%)	**11e** (60%)
6	Bn	*t*-Bu	**10f** (97%)	**11f** (67%)
7	Bn	*i*-Pr	**10g** (95%)	**11g** (82%)
8	Bn	Bn	**10h** (96%)	**11h** (45%)

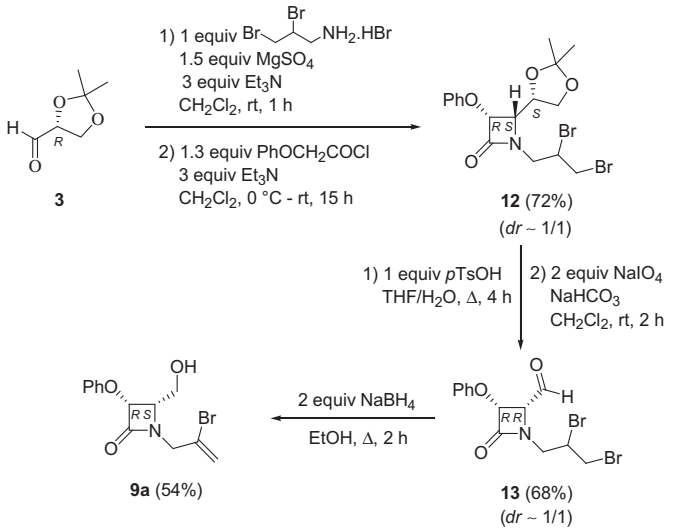
In order to assess the chiral purity of vinyl bromides **11**, compound **11a** was treated with 2 equiv of Pirkle alcohol prior to ^1H NMR analysis ($CDCl_3$), pointing to an enantiomeric ratio of 94/6. This observation confirms the preservation of the enantiomeric purity throughout the reaction sequence, and corroborates the importance of 4-imidoylazetidin-2-ones **10** as synthons for the preparation of chiral target compounds.

In view of the surprising conversion of 1-allyl-β-lactams **5e**–**g** and **10a**–**h** into vinyl bromides **9a**–**c** and **11a**–**h**, as well as in order to support the proposed reaction mechanism that indeed



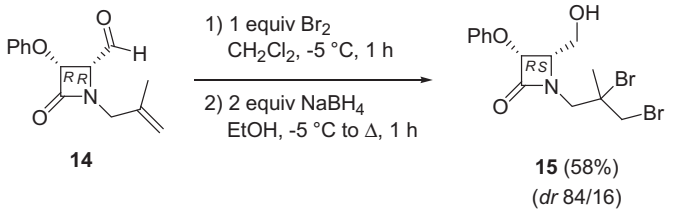
Scheme 3.

dibrominated intermediates are formed, the preparation of (3*R*,4*R*)-1-(2,3-dibromopropyl)-4-formylazetidin-2-one **13** was accomplished analogous to the synthesis of β-lactams **5a**–**d**.[6,7] Thus, condensation of (*R*)-glyceraldehyde acetonide **3** with the hydrobromide salt of 2,3-dibromopropylamine in the presence of Et_3N, and Staudinger reaction of the resulting imine using phenoxyacetyl chloride afforded a diastereomeric mixture of azetidin-2-one **12** (*dr* ~1/1, based on ^1H NMR analysis), which was further converted into (3*R*,4*R*)-1-(2,3-dibromopropyl)-4-formylazetidin-2-one **13** through hydrolysis and subsequent oxidation. Reduction of aldehyde **13** with 2 equiv of $NaBH_4$ in EtOH under reflux afforded (3*R*,4*S*)-1-(2-bromo-2-propenyl)-4-hydroxymethyl-3-phenoxyazetidin-2-one **9a** as the sole reaction product (Scheme 4).



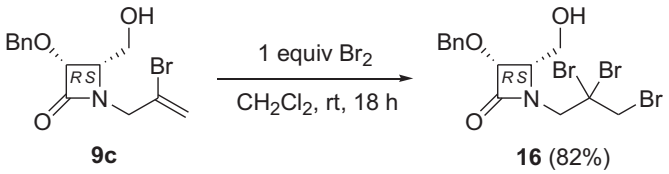
Scheme 4.

Additional proof for the proposed intramolecular dehydrobromination protocol was provided through the bromination of (3*R*,4*R*)-4-formyl-1-(2-methyl-2-propenyl)-β-lactam **14**, prepared according to a literature procedure starting from 2-methyl-2-propenylamine,[12] in CH_2Cl_2 at −5 °C and subsequent reduction with $NaBH_4$ in EtOH (Scheme 5). As there is no proton available for deprotonation at the C2-atom of the 2,3-dibromopropyl moiety, the result of the reaction was expected to be a diastereomeric mixture of (3*R*,4*S*)-1-(2,3-dibromo-2-methylpropyl)-4-hydroxymethyl-3-phenoxyazetidin-2-ones **15**. ^1H NMR analysis ($CDCl_3$) revealed that indeed the latter β-lactam **15** was formed in a diastereomeric ratio of 84/16, from which only the major isomer could be isolated in pure form through column chromatography on silica gel (Scheme 5).



Scheme 5.

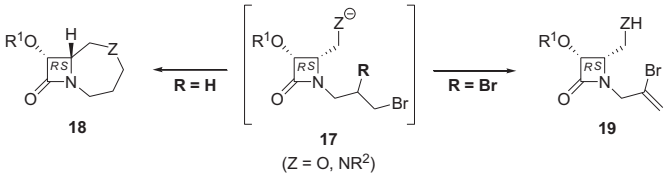
Although no aza- and oxaheterocyclic annulated β-lactams could be prepared via bromination of 1-allyl-β-lactams and subsequent reduction, the synthesized azetidin-2-ones **9a**–**c** and **11a**–**h** comprise an interesting class of compounds. As vinyl bromides in general are useful intermediates for carbon–carbon and carbon–heteroatom bond formation by transition metal-catalyzed coupling reactions,[13] chiral β-lactams **9a**–**c** and **11a**–**h** could be of interest as building blocks toward novel biologically active compounds. Furthermore, further elaboration of the double bond in azetidin-2-one **9c** was achieved using 1 equiv of bromine in dichloromethane at room temperature for 18 h, affording 1-(2,2,3-tribromopropyl)-β-lactam **16** in 82% yield (Scheme 6).



Scheme 6.

It should be noted that a totally different yet selective reactivity is observed for anions **17**, obtained as intermediates through reduction of the corresponding aldehydes or imines, depending on the substitution pattern of the *N*-side chain. Apparently, a clean 7-*exo*-*tet*-cyclization to bicycles **18** occurs when R=H, whereas dehydrobromination to vinyl bromides **19** prevails when R=Br (Scheme 7). Despite the increased steric hindrance due to the additional bromine atom, the increased acidity of the proton at C2 of the *N*-alkyl moiety and the decreased electrophilicity of the bromomethyl group in intermediates **17** control the reaction pathway giving rise to deprotonation instead of cyclization when R=Br.

In conclusion, a new and straightforward approach toward chiral functionalized piperazines and 1,4-diazepanes via ring opening of piperazine and 1,4-diazepane annulated β-lactams, derived from (3*R*,4*R*)-4-formyl-1-(ω-haloalkyl)azetidin-2-ones, has been presented. However, an attempt to extend this methodology toward the use of (3*R*,4*R*)-1-allyl-4-formylazetidin-2-ones as starting compounds unexpectedly resulted in the selective formation of synthetically interesting (3*R*,4*S*)-1-(2-bromo-2-propenyl)-β-lactams via a reductive dehydrobromination protocol.



Scheme 7.

3. Experimental part

3.1. Synthesis of methyl (*R*)-[(*S*)-piperazin-2-yl]acetates 7a–d and methyl (*R*)-2-[(*S*)-1,4-diazepan-2-yl]acetates 7e–i

As a representative example, the synthesis of methyl (*R*)-benzyloxy-[(*S*)-4-(1-methylethyl)piperazin-2-yl]acetate **7d** is described.

To an ice-cooled solution of (6*S*,7*R*)-7-benzyloxy-4-(1-methylethyl)-1,4-diazabicyclo[4.2.0]octan-8-one **6d**[7] (0.67 g, 2.4 mmol, 1 equiv) in MeOH (10 mL) was added dropwise a saturated solution of HCl in MeOH (40 mL). After stirring for 1 h at 0 °C, the resulting reaction mixture was warmed to room temperature and further stirred for 15 h. Subsequently, a saturated $NaHCO_3$ solution was added till pH 7.0. After vigorous stirring for 30 min, the reaction mixture was extracted with CH_2Cl_2 (4×30 mL) and the combined organic phases were dried over $MgSO_4$. After filtration of the drying agent, evaporation of the solvent in vacuo and purification via column

chromatography on silica gel, pure methyl (*R*)-benzyloxy-[(*S*)-4-(1-methylethyl)piperazin-2-yl]acetate **7d** was obtained in 71% yield.

3.1.1. Methyl (R)-[(S)-4-allylpiperazin-2-yl]methoxyacetate ***7a***. Brown oil. R_f=0.08 (CH_2Cl_2/MeOH 95/5). Yield 66%. $[\alpha]_D$ +24.2 (*c* 0.95, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.93–2.07 (3H, m), 2.68–2.78 (2H, m), 2.84 (1H, d×d×d, *J*=12.1, 10.6, 2.9 Hz), 2.93–3.02 (3H, m), 3.08 (1H, d×d×d, *J*=9.5, 6.6, 2.9 Hz), 3.41 (3H, s), 3.72 (1H, d, *J*=6.6 Hz), 3.78 (3H, s), 5.13–5.22 (2H, m) 5.84 (1H, d×d×t, *J*=17.2, 10.3, 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.95, 51.82, 53.64, 55.24, 56.58, 58.55, 62.10, 82.26, 117.85, 134.92, 171.31. IR (NaCl, cm^{-1}): ν_{NH}=3347; $\nu_{C=O}$=1753; ν_{max}=3076, 2948, 2827, 1643, 1459, 1438, 1331, 1271, 1198, 1118, 1010. MS (70 eV): *m*/*z* (%) 229 (M^++1, 100).

3.1.2. Methyl (R)-[(S)-4-benzylpiperazin-2-yl]methoxyacetate ***7b***. Brown oil. R_f=0.11 (CH_2Cl_2/MeOH 95/5). Yield 70%. $[\alpha]_D$ +19.9 (*c* 1.66, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99–2.10 (2H, m), 2.17 (1H, br s), 2.64–2.68 (2H, m), 2.80 (1H, d×d×d, *J*=12.1, 10.5, 2.9 Hz), 2.94 (1H, d×d×d, *J*=12.1, 3.3, 3.0 Hz), 3.08 (1H, d×d×d, *J*=9.4, 6.2, 2.8 Hz), 3.38 (3H, s), 3.45 and 3.50 (2×1H, 2×d, *J*=13.1 Hz), 3.69 (3H, s), 3.72 (1H, d, *J*=6.2 Hz), 7.19–7.30 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.81, 51.82, 53.62, 55.30, 56.55, 58.61, 63.36, 82.05, 126.98, 128.13, 129.06, 137.93, 171.51. IR (NaCl, cm^{-1}): ν_{NH}=3343; $\nu_{C=O}$=1752; ν_{max}=2948, 2826, 1494, 1454, 1335, 1268, 1198, 1118, 1027, 1011. MS (70 eV): *m*/*z* (%) 279 (M^++1, 100).

3.1.3. Methyl (R)-methoxy-[(S)-4-(1,1-dimethylethyl)piperazin-2-yl] acetate ***7c***. Brown oil. R_f=0.05 (CH_2Cl_2/MeOH 95/5). Yield 63%. $[\alpha]_D$ +39.1 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s), 2.15–2.29 (2H, m), 2.83–2.90 (3H, m), 3.02 (1H, d×d×d, *J*=12.1, 3.4, 3.4 Hz), 3.10–3.14 (1H, m), 3.42 (3H, s), 3.77 (1H, d, *J*=5.2 Hz), 3.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.71, 45.38, 46.28, 48.11, 51.99, 54.74, 56.92, 58.77, 82.26, 171.64. IR (NaCl, cm^{-1}): ν_{NH}=3340; $\nu_{C=O}$=1746; ν_{max}=2973, 2831, 1458, 1437, 1361, 1279, 1204, 1115, 1018. MS (70 eV): *m*/*z* (%) 245 (M^++1, 100).

3.1.4. Methyl (R)-benzyloxy-[(S)-4-(1-methylethyl)piperazin-2-yl]acetate ***7d***. Brown oil. R_f=0.05 (CH_2Cl_2/MeOH 95/5). Yield 71%. $[\alpha]_D$ +32.2 (*c* 0.53, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 and 1.02 (2×3H, 2×d, *J*=6.2 Hz), 2.13–2.24 (2H, m), 2.33 (1H, br s), 2.60–2.71 (3H, m), 2.80 (1H, d×d×d, *J*=12.0, 10.5, 3.0 Hz), 2.97 (1H, d×d×d, *J*=12.0, 3.0, 3.0 Hz), 3.11 (1H, d×d×d, *J*=9.4, 6.4, 2.9 Hz), 3.75 (3H, s), 3.95 (1H, d, *J*=6.4 Hz), 4.43 and 4.69 (2×1H, 2×d, *J*=11.6 Hz), 7.26–7.35 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.76, 18.54, 45.27, 48.92, 51.01, 51.91, 54.80, 56.87, 73.00, 80.05, 128.07, 128.33, 128.42, 137.08, 171.64. IR (NaCl, cm^{-1}): ν_{NH}=3344; $\nu_{C=O}$=1751; ν_{max}=2964, 2818, 1455, 1437, 1332, 1268, 1203, 1181, 1140, 1114, 1060, 1019. MS (70 eV): *m*/*z* (%) 307 (M^++1, 100).

3.1.5. Methyl (R)-[(S)-4-benzyl-1,4-diazepan-2-yl]methoxyacetate ***7e***. Brown oil. R_f=0.10 (CH_2Cl_2/MeOH 95/5). Yield 68%. $[\alpha]_D$ +17.2 (*c* 0.64, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59–1.83 (2H, m), 1.98 (1H, br s, NH), 2.53–2.63 (2H, m), 2.70–2.80 (2H, m), 2.84 (1H, d×d×d, *J*=13.8, 8.0, 4.1 Hz), 3.03 (1H, d×d×d, *J*=13.8, 6.7, 4.6 Hz), 3.19 (1H, d×d×d, *J*=8.8, 5.5, 3.3 Hz), 3.36 (3H, s), 3.61 (1H, d, *J*=13.5 Hz), 3.65 (1H, d, *J*=5.5 Hz), 3.66 (3H, s), 3.70 (1H, d, *J*=13.5 Hz), 7.19–7.35 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.10, 45.79, 51.77, 54.58, 58.69, 60.06, 62.65, 83.23, 126.83, 128.16, 128.68, 139.57, 171.80. IR (NaCl, cm^{-1}): ν_{NH}=3350; $\nu_{C=O}$=1751; ν_{max}=2933, 2829, 1494, 1454, 1436, 1352; 1269, 1196, 1121, 1072, 1029. MS (70 eV): *m*/*z* (%) 293 (M^++1, 100).

3.1.6. Methyl (R)-[(S)-4-allyl-1,4-diazepan-2-yl]methoxyacetate ***7f***. Brown oil. R_f=0.06 (CH_2Cl_2/MeOH 95/5). Yield 69%. $[\alpha]_D$ +16.6 (*c* 0.48, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62–1.85 (2H, m), 2.26 (1H, br s), 2.53–2.62 (2H, m), 2.73–2.87 (3H, m), 3.03 (1H, d×d×d, *J*=13.8, 6.6, 4.7 Hz), 3.12 (1H, d×d×t, *J*=13.6, 6.6, 1.2 Hz), 3.12–3.19 (1H, m), 3.20 (1H, d×d×d, *J*=8.8, 5.4, 3.6 Hz), 3.41 (3H, s), 3.70 (1H, d, *J*=5.4 Hz), 3.77 (3H, s), 5.11–5.20 (2H, m), 5.86 (1H, d×d×t, *J*=17.0, 10.2, 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.90, 45.68, 51.91, 54.71, 58.26, 58.78, 59.67, 61.67, 83.12, 117.53, 135.79, 171.78. IR (NaCl, cm^{-1}): ν_{NH}=3350; $\nu_{C=O}$=1751; ν_{max}=2933, 2830, 1642, 1459, 1437, 1346, 1272, 1197, 1122, 998. MS (70 eV): *m*/*z* (%) 243 (M^++1, 100).

3.1.7. Methyl (R)-methoxy-[(S)-4-(1-methylethyl)-1,4-diazepan-2-yl] acetate ***7g***. Brown oil. R_f=0.03 (CH_2Cl_2/MeOH 93/7). Yield 47%. $[\alpha]_D$ +15.2 (*c* 0.40, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 and 1.08 (2×3H, 2×d, *J*=6.6 Hz), 1.58–1.90 (2H, m), 2.62–2.72 (2H, m), 2.76–2.89 (3H, m), 2.97–3.06 (2H, m), 3.22–3.28 (1H, m), 3.42 (3H, s), 3.75 (1H, d, *J*=5.2 Hz), 3.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.48, 18.80, 31.09, 45.54, 50.35, 51.96, 54.46, 56.22, 58.83, 59.73, 83.04, 171.74. IR (NaCl, cm^{-1}): ν_{NH}=3353; $\nu_{C=O}$=1753; ν_{max}=2927, 2854, 1460, 1361, 1270, 1196, 1122. MS (70 eV): *m*/*z* (%) 245 (M^++1, 100).

3.1.8. Methyl (R)-benzyloxy-[(S)-4-(1,1-dimethylethyl)-1,4-diazepan-2-yl]acetate ***7h***. Brown oil. R_f=0.07 (CH_2Cl_2/MeOH 95/5). Yield 64%. $[\alpha]_D$ +27.2 (*c* 0.66, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (9H, s), 1.85–1.96 and 1.99–2.14 (2×1H, 2×m), 2.81–2.88 (2H, m), 2.92–2.95 and 2.99–3.04 (2×1H, 2×m), 3.05–3.25 (2H, m), 3.50–3.62 (1H, m), 3.78 (3H, s), 3.99 (1H, d, *J*=4.6 Hz), 4.42 and 4.79 (2×1H, 2×d, *J*=11.7 Hz), 7.29–7.36 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.65, 29.36, 45.33, 48.51, 52.16, 57.79, 60.58, 72.84, 79.81, 128.16, 128.40, 128.50, 137.02, 171.28. IR (NaCl, cm^{-1}): ν_{NH}=3296; $\nu_{C=O}$=1749; ν_{max}=2953, 2721, 2608, 1455, 1436, 1269, 1206, 1120, 1028. MS (70 eV): *m*/*z* (%) 335 (M^++1, 100).

3.1.9. Methyl (R)-((S)-4-allyl-1,4-diazepan-2-yl)benzyloxyacetate ***7i***. Brown oil. R_f=0.04 (CH_2Cl_2/MeOH 95/5). Yield 63%. $[\alpha]_D$ +44.9 (*c* 1.40, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59–1.83 (2H, m), 2.33 (1H, br s), 2.50–2.61 (2H, m), 2.71–2.83 (3H, m), 2.99 (1H, d×d×d, *J*=13.8, 6.9, 4.4 Hz), 3.04–3.19 (2H, m), 3.24 (1H, d×d×d, *J*=8.7, 5.0, 3.5 Hz), 3.74 (3H, s), 3.89 (1H, d, *J*=5.0 Hz), 4.39 and 4.73 (2×1H, 2×d, *J*=11.6 Hz), 5.08–5.19 (2H, m), 5.83 (1H, d×d×t, *J*=17.0, 10.2, 6.5 Hz), 7.25–7.42 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.93, 45.67, 51.82, 54.61, 58.54, 59.65, 61.55, 72.75, 80.49, 117.34, 127.92, 128.16, 128.34, 135.92, 137.25, 171.86. IR (NaCl, cm^{-1}): ν_{NH}=3348; $\nu_{C=O}$=1751; ν_{max}=2930, 1699, 1642, 1497, 1455, 1344, 1271, 1205, 1165, 1113, 1027. MS (70 eV): *m*/*z* (%) 319 (M^++1, 100).

3.2. Synthesis of (3*R*,4*S*)-1-allyl-4-imidoyl-β-lactams 10

As a representative example, the synthesis of (3*R*,4*S*)-1-allyl-3-benzyloxy-4-{(*E*)-[((1,1-dimethylethyl)imino)methyl]}azetidin-2-one **10f** is described. In a 100 mL flask, (3*R*,4*R*)-1-allyl-3-benzyloxy-4-formylazetidin-2-one **5c** (0.91 g, 3.7 mmol, 1 equiv) was dissolved in CH_2Cl_2 (50 mL) and $MgSO_4$ (0.71 g, 5.6 mmol, 1.5 equiv) was added. Subsequently, *tert*-butylamine (0.25 g, 3.7 mmol, 1 equiv) was added and the resulting reaction mixture was stirred at room temperature for 1 h. After filtration of $MgSO_4$, the solvent was evaporated in vacuo, yielding 4-imidoylazetidin-2-one **10f** (1.08 g, 97%).

All the imines **10** were obtained in high purity (>95% based on NMR) and used as such in the next reaction step due to their hydrolytic instability.

3.2.1. (3R,4S)-1-Allyl-4-{(E)-[((1,1-dimethylethyl)imino)methyl]}-3-phenoxyazetidin-2-one ***10a***. Colorless oil. Yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (9H, s), 3.94 (2H, d×t, *J*=6.6, 1.2 Hz), 4.45 (1H, d×d, *J*=6.9, 4.5 Hz), 5.20–5.30 (2H, m), 5.40 (1H, d, *J*=4.5 Hz), 5.70–5.90 (1H, m), 6.89–7.01 and 7.22–7.32 (3H and 2H, 2×m), 7.53 (1H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 29.17, 44.21, 58.12, 62.04, 81.42, 115.30, 119.97, 122.38, 129.60, 131.16, 154.80,

156.71, 164.89. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1761; $\nu_{C=N}$=1667; $\nu_{C=C}$=1644; ν_{max}=2967, 2930, 1598, 1495, 1397, 1233, 752, 690. MS (70 eV): *m*/*z* (%) 287 (M^++1, 100).

3.2.2. (3R,4S)-1-Allyl-4-{(E)-[((1-methylethyl)imino)methyl]}-3-phenoxyazetidin-2-one ***10b***. Colorless oil. Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 and 1.10 (2×3H, 2×d, *J*=6.3 Hz, $(CH_3)_2$), 3.29 (1H, sept, *J*=6.3 Hz), 3.87–4.03 (2H, m), 4.44 (1H, d×d, *J*=7.0, 4.6 Hz), 5.22–5.28 (2H, m), 5.38 (1H, d, *J*=4.6 Hz), 5.70–5.88 (1H, m), 6.92–7.16 and 7.23–7.34 (3H and 2H, 2×m), 7.61 (1H, d, *J*=7.0 Hz). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 23.52, 23.69, 44.18, 61.34, 61.51, 81.57, 115.41, 120.00, 122.47, 129.64, 131.04, 156.83, 157.26, 164.90. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1760; $\nu_{C=N}$=1666; $\nu_{C=C}$=1644; ν_{max}=2967, 2928, 1598, 1494, 1396, 1232, 753, 690. MS (70 eV): *m*/*z* (%) 273 (M^++1, 100).

3.2.3. (3R,4S)-1-Allyl-4-{(E)-[(benzylimino)methyl]}-3-phenoxyazetidin-2-one ***10c***. Colorless oil. Yield 97%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84–3.92 and 3.97–4.06 (2×1H, 2×m), 4.50 (1H, d×d, *J*=13.5, 1.2 Hz), 4.53 (1H, d×d, *J*=6.6, 4.6 Hz), 4.61 (1H, d×d, *J*=13.5, 1.2 Hz), 5.18–5.30 (2H, m), 5.40 (1H, d, *J*=4.6 Hz), 5.68–5.82 (1H, m), 6.93–7.12 and 7.21–7.35 (4H and 6H, 2×m), 7.73 (1H, d×t, *J*=6.6, 1.2 Hz). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 44.16, 61.16, 65.07, 81.72, 115.47, 119.91, 122.60, 127.31, 128.14, 128.64, 129.77, 130.98, 137.79, 156.98, 160.89, 164.97. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1758; $\nu_{C=N}$=1667; $\nu_{C=C}$=1645; ν_{max}=2919, 1598, 1494, 1397, 1232, 752, 736, 691. MS (70 eV): *m*/*z* (%) 321 (M^++1, 100).

3.2.4. (3R,4S)-1-Allyl-3-methoxy-4-{(E)-[((1,1-dimethylethyl)imino)methyl]}azetidin-2-one ***10d***. Colorless oil. Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s), 3.43 (3H, s), 3.85–3.89 (2H, m), 4.22 (1H, d×d, *J*=6.9, 4.7 Hz), 4.66 (1H, d, *J*=4.7 Hz), 5.16–5.18 and 5.21–5.23 (2×1H, 2×m), 5.66–5.79 (1H, m), 7.59 (1H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 29.51, 43.91, 58.12, 58.87, 61.88, 85.63, 119.63, 131.44, 156.05, 166.49. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1757; $\nu_{C=N}$=1668; $\nu_{C=C}$=1645; ν_{max}=2967, 2932, 1394, 1212, 1035. MS (70 eV): *m*/*z* (%) 225 (M^++1, 49).

3.2.5. (3R,4S)-1-Allyl-3-methoxy-4-{(E)-[((1-methylethyl)imino)methyl]}azetidin-2-one ***10e***. Colorless oil. Yield 98%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (6H, d, *J*=6.3 Hz), 3.41–3.54 (1H, m), 3.45 (3H, s), 3.84 (1H, d×d, *J*=15.8, 6.4 Hz), 3.91 (1H, d×d, *J*=15.8, 5.6 Hz), 4.22 (1H, d×d, *J*=6.9, 4.7 Hz), 4.65 (1H, d, *J*=4.7 Hz), 5.18–5.19 and 5.22–5.23 (2×1H, 2×m), 5.66–5.79 (1H, m), 7.64 (1H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 23.89, 23.96, 43.87, 58.94, 61.07, 61.48, 85.56, 119.68, 131.28, 158.45, 166.49. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1756; $\nu_{C=N}$=1666; $\nu_{C=C}$=1644; ν_{max}=2967, 2931, 1383, 1211, 1149, 1033, 930. MS (70 eV): *m*/*z* (%) 211 (M^++1, 100).

3.2.6. (3R,4S)-1-Allyl-3-benzyloxy-4-{(E)-[((1,1-dimethylethyl)imino)methyl]}azetidin-2-one ***10f***. Colorless oil. Yield 97%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s), 3.86 (2H, d, *J*=6.3 Hz), 4.23 (1H, d×d, *J*=6.9, 4.5 Hz), 4.59 and 4.67 (2×1H, 2×d, *J*=11.8 Hz), 4.83 (1H, d, *J*=4.5 Hz), 5.15–5.22 (2H, m), 5.65–5.79 (1H, m), 7.27–7.39 (5H, m), 7.62 (1H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.38, 43.79, 61.71, 72.69, 83.27, 119.44, 127.64, 127.99, 128.42, 131.37, 136.59, 155.92, 166.56. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1766; $\nu_{C=N}$=1668; $\nu_{C=C}$=1645; ν_{max}=2969, 1531, 1498, 1455, 1394, 1213, 739, 699. MS (70 eV) *m*/*z* (%): 301 (M^++1, 100).

3.2.7. (3R,4S)-1-Allyl-3-benzyloxy-4-{(E)-[((1-methylethyl)imino)methyl]}azetidin-2-one ***10g***. Colorless oil. Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (6H, d, *J*=6.3 Hz), 3.42 (1H, sept, *J*=6.3 Hz), 3.79–3.94 (2H, m), 4.21 (1H, d×d, *J*=6.9, 4.7 Hz), 4.62 and 4.70 (2×1H, 2×d, *J*=11.8 Hz), 4.83 (1H, d, *J*=4.7 Hz), 5.12–5.17 (2H, m), 5.65–5.79 (1H, m), 7.28–7.38 (5H, m), 7.66 (1H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.82, 43.77, 60.97, 61.30, 72.81, 83.20, 119.49, 127.82, 128.10, 128.47, 131.24, 136.56, 158.42, 166.56. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1767; $\nu_{C=N}$=1668; $\nu_{C=C}$=1645; ν_{max}=2968, 1529, 1498, 1455, 1396, 1157, 739, 699. MS (70 eV) *m*/*z* (%): 287 (M^++1, 100).

3.2.8. (3R,4S)-1-Allyl-3-benzyloxy-4-{(E)-[(benzylimino)methyl]}azetidin-2-one ***10h***. Colorless oil. Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (1H, d×d, *J*=15.4, 6.2 Hz), 3.91 (1H, d×d, *J*=15.4, 5.6 Hz), 4.27 (1H, d×d, *J*=6.4, 4.7 Hz), 4.54–4.61 (3H, m), 4.70 (1H, d, *J*=11.8 Hz), 4.82 (1H, d, *J*=4.7 Hz), 5.10–5.17 (2H, m), 5.61–5.75 (1H, m), 7.20–7.33 (10H, m), 7.72 (1H, d, *J*=6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.76, 60.80, 65.03, 72.94, 83.27, 119.38, 127.90, 128.07, 128.54, 131.12, 136.53, 138.12, 161.95, 166.47. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1767; $\nu_{C=N}$=1669; $\nu_{C=C}$=1645; ν_{max}=3030, 2909, 2870, 1604, 1524, 1496, 1454, 1397, 1027, 738, 699. MS (70 eV) *m*/*z* (%): 335 (M^++1, 100).

3.3. Synthesis of (3*R*,4*S*)-1-(2-bromo-2-propenyl)azetidin-2-ones 9 and 11

As a representative example, the synthesis of (3*R*,4*S*)-1-(2-bromo-2-propenyl)-4-[(1,1-dimethylethylamino)methyl]-3-phenoxyazetidin-2-one **11a** is described. In a two-necked flask of 100 mL, 4-imidoyl-β-lactam **10a** (4.1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10 mL), and the mixture was placed under N_2 atmosphere at −78 °C. A solution of bromine (0.65 g, 4.1 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) was added dropwise, and the resulting mixture was stirred for 2 h at −78 °C. Subsequently, $NaBH_4$ (0.32 g, 8.2 mmol, 2 equiv) and EtOH (50 mL) were added, and the reaction mixture was allowed to warm to room temperature. After 15 min, the reaction mixture was heated under reflux for 1 h. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated in vacuo. Further purification was performed by column chromatography on silica gel, yielding pure (3*R*,4*S*)-1-(2-bromo-2-propenyl)-4-[(1,1-dimethylethylamino)methyl]-3-phenoxyazetidin-2-one **11a** in 74% yield. An analogous procedure was applied for the synthesis of compounds **9**.

3.3.1. (3R,4S)-1-(2-Bromo-2-propenyl)-4-hydroxymethyl-3-phenoxyazetidin-2-one ***9a***. Light-yellow oil. R_f=0.24 (hexane/EtOAc 3/2). Yield 74%. $[\alpha]_D$ +45 (*c* 1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (1H, br s), 3.98–4.03 (2H, m), 4.00 (1H, d, *J*=15.7 Hz), 4.08–4.12 (1H, m), 4.47 (1H, d, *J*=15.7 Hz), 5.37 (1H, d, *J*=5.0 Hz), 5.67 (1H, d, *J*=1.8 Hz), 5.92 (1H, d×d, *J*=1.8, 0.8 Hz), 7.03–7.11 and 7.29–7.35 (3H and 2H, 2×m). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 49.13, 58.27, 60.01, 81.13, 115.77, 120.81, 122.98, 126.80, 129.88, 157.21, 165.85. IR (NaCl, cm^{-1}): ν_{OH}=3436; $\nu_{C=O}$=1744; $\nu_{C=C}$=1630; ν_{max}=2924, 1590, 1400, 1232, 1045, 753, 690. MS (70 eV): *m*/*z* (%) 312/4 (M^++1, 100).

3.3.2. (3R,4S)-1-(2-Bromo-2-propenyl)-4-hydroxymethyl-3-methoxyazetidin-2-one ***9b***. Light-yellow oil. R_f=0.13 (hexane/EtOAc 1/1). Yield 65%. $[\alpha]_D$ +38.2 (*c* 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (1H, br s), 3.63 (3H, s), 3.87–3.99 (4H, m), 4.39 (1H, d, *J*=16.0 Hz), 4.64 (1H, d, *J*=4.4 Hz), 5.63 (1H, d, *J*=1.7 Hz), 5.87–5.89 (1H, m). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.59, 57.77, 59.60, 59.68, 84.32, 120.41, 126.93, 167.39. IR (NaCl, cm^{-1}): ν_{OH}=3420; $\nu_{C=O}$=1750; $\nu_{C=C}$=1631; ν_{max}=2923, 1459, 1265, 1046, 736, 704. MS (70 eV): *m*/*z* (%) 250/2 (M^++1, 20).

3.3.3. (3R,4S)-3-Benzyloxy-1-(2-bromo-2-propenyl)-4-hydroxymethylazetidin-2-one ***9c***. Colorless oil. Yield 59%. R_f=0.25 (hexane/EtOAc 3/2). $[\alpha]_D$ +38 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83–3.86 (3H, m), 3.89 and 4.40 (2×1H, 2×d, *J*=16.0 Hz), 4.70 (1H, d, *J*=11.7 Hz), 4.81 (1H, d, *J*=4.7 Hz), 4.95 (1H, d,

J=11.7 Hz), 5.62 (1H, d, J=1.9 Hz), 5.86 (1H, d×t, J=1.9, 1.1 Hz), 7.30–7.41 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.58, 57.97, 59.65, 73.56, 81.85, 120.28, 126.83, 128.16, 128.39, 128.65, 136.47, 167.43. IR (NaCl, cm^{-1}): ν_{OH}=3419; $\nu_{C=O}$=1756; $\nu_{C=C}$=1631; ν_{max}=2928, 2875, 1671, 1497, 1455. MS (70 eV) m/z (%): 326/8 (M^++1, 100).

3.3.4. (3R,4S)-1-(2-Bromo-2-propenyl)-4-[(1,1-dimethylethylamino) methyl]-3-phenoxyazetidin-2-one ***11a***. White crystals. Mp 70 °C. R_f=0.18 (CH_2Cl_2/MeOH 95/5). Yield 71%. $[\alpha]_D$ +54.5 (c 1.79, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (9H, s), 2.90 (1H, d×d, J=11.9, 5.9 Hz), 3.00 (1H, d×d, J=11.9, 6.3 Hz), 4.01–4.07 (1H, m), 4.09 and 4.38 (2×1H, 2×d, J=15.6 Hz), 5.33 (1H, d, J=5.0 Hz), 5.66 and 5.88 (2×1H, 2×d, J=1.5 Hz), 7.00–7.09 and 7.28–7.33 (3H and 2H, 2×m). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 28.97, 41.55, 49.22, 50.55, 58.55, 80.55, 115.56, 120.52, 122.44, 127.25, 129.74, 157.55, 166.14. IR (KBr, cm^{-1}): ν_{NH}=3324; $\nu_{C=O}$=1758; $\nu_{C=C}$=1630; ν_{max}=2963, 1591, 1494, 1234, 753, 734, 690. MS (70 eV): m/z (%) 367/9 (M^++1, 100). HRMS (ESI) calcd for $C_{17}H_{24}BrN_2O_2$ 367.1021 $[M+H]^+$, found 367.1003.

3.3.5. (3R,4S)-1-(2-Bromo-2-propenyl)-4-[(1-methylethylamino) methyl]-3-phenoxyazetidin-2-one ***11b***. Yellow oil. R_f=0.04 (CH_2Cl_2/MeOH 97/3). Yield 62%. $[\alpha]_D$ +113.9 (c 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 and 1.46 (2×3H, 2×d, J=6.1 Hz), 3.34–3.41 (3H, m), 4.21 and 4.34 (2×1H, 2×d, J=15.4 Hz), 4.62–4.68 (1H, m), 5.47 (1H, d, J=5.0 Hz), 5.66 (1H, d, J=2.1 Hz), 6.09 (1H, d×d, J=2.1, 1.1 Hz), 7.02–7.07, 7.19–7.22 and 7.27–7.35 (1H, 2H and 2H, 3×m). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 19.49, 19.66, 42.24, 49.45, 51.72, 54.59, 81.50, 116.43, 122.40, 123.13, 126.70, 129.88, 156.86, 165.70. IR (NaCl, cm^{-1}): ν_{NH}=3406; $\nu_{C=O}$=1762; $\nu_{C=C}$=1630; ν_{max}=2941, 1592, 1494, 1934, 1234, 909, 754, 727, 690. MS (70 eV): m/z (%) 353/5 (M^++1, 100).

3.3.6. (3R,4S)-4-[(Benzylamino)methyl]-1-(2-bromo-2-propenyl)-3-phenoxyazetidin-2-one ***11c***. Yellow oil. R_f=0.48 (CH_2Cl_2/MeOH 95/5). Yield 48%. $[\alpha]_D$ +38.7 (c 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (1H, d×d, J=12.9, 6.2 Hz), 3.05 (1H, d×d, J=12.9, 5.9 Hz), 3.78 (2H, s), 4.02 (1H, d, J=15.7 Hz), 4.06–4.12 (1H, m), 4.40 (1H, d, J=15.7 Hz), 5.32 (1H, d, J=4.6 Hz), 5.61 (1H, d, J=1.8 Hz), 5.78 (1H, d×d, J=1.8, 0.8 Hz), 7.00–7.06 and 7.24–7.33 (3H and 7H, 2×m). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 47.62, 49.17, 54.18, 57.48, 80.64, 115.60, 120.55, 122.52, 127.36, 128.20, 128.61, 129.77, 139.61, 157.45, 165.99. IR (NaCl, cm^{-1}): ν_{NH}=3319; $\nu_{C=O}$=1756; $\nu_{C=C}$=1630; ν_{max}=2926, 1590, 1494, 1235, 908, 752, 730, 691. MS (70 eV): m/z (%) 401/3 (M^++1, 100).

3.3.7. (3R,4S)-1-(2-Bromo-2-propenyl)-3-methoxy-4-[(1,1-dimethylethylamino)methyl]-azetidin-2-one ***11d***. Light-yellow oil. R_f=0.21 (CH_2Cl_2/MeOH 95/5). Yield 64%. $[\alpha]_D$ +63.4 (c 0.97, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s), 2.62 (1H, br s), 2.86 (1H, d×d, J=11.8, 5.8 Hz), 2.93 (1H, d×d, J=11.8, 6.9 Hz), 3.59 (3H, s), 3.83–3.91 (1H, m), 4.03 and 4.28 (2×1H, 2×d, J=16.0 Hz), 4.59 (1H, d, J=5.0 Hz), 5.63 (1H, d, J=2.2 Hz), 5.86 (1H, s). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 28.64, 41.26, 48.88, 51.29, 57.78, 59.42, 83.94, 120.29, 127.42, 167.81. IR (NaCl, cm^{-1}): ν_{NH}=3310; $\nu_{C=O}$=1750; $\nu_{C=C}$=1630; ν_{max}=2960, 2930, 1389, 1213, 1117, 1049. MS (70 eV): m/z (%) 305/7 (M^++1, 100). HRMS (ESI) calcd for $C_{12}H_{22}BrN_2O_2$ 305.0865 $[M+H]^+$, found 305.0852.

3.3.8. (3R,4S)-1-(2-Bromo-2-propenyl)-3-methoxy-4-[(1-methylethylamino)methyl]azetidin-2-one ***11e***. Light-yellow oil. R_f=0.13 (CH_2Cl_2/MeOH 95/5). Yield 60%. $[\alpha]_D$ +67.1 (c 1.26, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (6H, d, J=6.1 Hz), 3.08–3.22 (3H, m), 3.65 (3H, s), 4.08 (1H, d, J=15.7 Hz), 4.19–4.23 (1H, m), 4.26 (1H, d, J=15.7 Hz), 4.72 (1H, d, J=4.4 Hz), 5.66 and 5.96 (2×1H, 2×d, J=2.2 Hz). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 20.61, 20.73, 43.40, 49.04, 50.71, 55.43, 59.62, 84.01, 121.27, 127.07, 167.58. IR (NaCl, cm^{-1}): ν_{NH}=3331; $\nu_{C=O}$=1753; $\nu_{C=C}$=1630; ν_{max}=2960, 2932, 1393, 1213, 1109, 1043. MS (70 eV): m/z (%) 291/3 (M^++1, 100). HRMS (ESI) calcd for $C_{11}H_{20}BrN_2O_2$ 291.0708 $[M+H]^+$, found 291.0713.

3.3.9. (3R,4S)-3-Benzyloxy-1-(2-bromo-2-propenyl)-4-[(1,1-dimethylethylamino)methyl]-azetidin-2-one ***11f***. Colorless oil. Yield 67%. R_f=0.15 (CH_2Cl_2/MeOH 95/5). $[\alpha]_D$ +23 (c 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (9H, s), 2.81 (1H, d×d, J=11.8, 5.8 Hz), 2.87 (1H, d×d, J=11.8, 6.6 Hz), 3.77–3.83 (1H, m), 4.00 and 4.28 (2×1H, 2×d, J=15.7 Hz), 4.68 (1H, d, J=11.8 Hz), 4.95 (1H, d, J=5.0 Hz), 4.91 (1H, d, J=11.8 Hz), 5.59 (1H, d, J=2.1 Hz), 5.82 (1H, d×d, J=2.1, 1.0 Hz), 7.28–7.36 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.84, 41.53, 48.74, 50.26, 58.13, 73.10, 81.73, 119.92, 127.38, 127.81, 127.98, 128.42, 137.08, 167.67. IR (NaCl, cm^{-1}): ν_{NH}=3311; $\nu_{C=O}$=1757; $\nu_{C=C}$=1630; ν_{max}=2964, 2867, 1455, 1392, 1232, 1027, 737, 699. MS (70 eV) m/z (%): 381/3 (M^++1, 100).

3.3.10. (3R,4S)-3-Benzyloxy-1-(2-bromo-2-propenyl)-4-[(1-methylethylamino)methyl]azetidin-2-one ***11g***. Colorless oil. Yield 82%. R_f=0.12 (CH_2Cl_2/MeOH 95/5). $[\alpha]_D$ +20 (c 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 and 1.02 (2×3H, 2×d, J=6.3 Hz), 2.75 (1H, sept, J=6.3 Hz), 2.87 (1H, d×d, J=12.1, 5.8 Hz), 2.94 (1H, d×d, J=12.1, 6.9 Hz), 3.83–3.89 (1H, m), 3.99 and 4.30 (2×1H, 2×d, J=15.7 Hz), 4.70 (1H, d, J=11.8 Hz), 4.76 (1H, d, J=5.0 Hz), 4.94 (1H, d, J=11.8 Hz), 5.61 (1H, d, J=2.0 Hz), 5.83 (1H, d×d, J=2.0, 1.0 Hz), 7.30–7.36 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.78, 22.89, 45.87, 48.80, 49.10, 57.61, 73.16, 81.78, 120.02, 127.34, 127.87, 128.05, 128.49, 137.08, 167.74. IR (NaCl, cm^{-1}): ν_{NH}=3336; $\nu_{C=O}$=1756; $\nu_{C=C}$=1631; ν_{max}=2963, 2928, 1674, 1455, 1398, 1110, 738, 699. MS (70 eV) m/z (%): 367/9 (M^++1, 100).

3.3.11. (3R,4S)-4-[(Benzylamino)methyl]-3-benzyloxy-1-(2-bromo-2-propenyl)azetidin-2-one ***11h***. Colorless oil. Yield 45%. R_f=0.5 (CH_2Cl_2/MeOH 95/5). $[\alpha]_D$ +35 (c 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (1H, br s), 2.87 (1H, d×d, J=12.4, 5.5 Hz), 2.94 (1H, d×d, J=12.4, 6.3 Hz), 3.75 (2H, s), 3.84–3.89 (1H, m), 3.91 and 4.30 (2×1H, 2×d, J=16.0 Hz), 4.67 (1H, d, J=11.6 Hz), 4.74 (1H, d, J=5.0 Hz), 4.90 (1H, d, J=11.6 Hz), 5.56 (1H, d, J=2.0 Hz), 5.74 (1H, d×d, J=2.0 Hz, J=1.0 Hz), 7.22–7.38 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.61, 48.69, 54.17, 57.18, 73.18, 81.75, 119.98, 127.06, 127.98, 128.04, 128.08, 128.42, 128.49, 136.99, 139.93, 167.66. IR (NaCl, cm^{-1}): ν_{NH}=3329; $\nu_{C=O}$=1758; $\nu_{C=C}$=1630; ν_{max}=2922, 1454, 1397, 1027, 738, 698. MS (70 eV) m/z (%): 415/7 (M^++1, 100).

3.4. Synthesis of (3*R*,4*R*)-1-(2,3-dibromopropyl)-4-formyl-3-phenoxyazetidin-2-one 13

The synthesis of (3*R*,4*R*)-1-(2,3-dibromopropyl)-4-formyl-3-phenoxyazetidin-2-one **13** was performed by means of a slightly modified four-step literature procedure using the hydrobromide salt of 2,3-dibromopropylamine as the starting material.[7] Compound **13** was obtained as a mixture of diastereomers (dr ~ 1/1).

3.4.1. (3R,4R)-1-(2,3-Dibromopropyl)-4-formyl-3-phenoxyazetidin-2-one ***13***. Spectral data of one isomer isolated by column chromatography (SiO_2). Light-yellow oil. Yield 68%. R_f=0.28 (hexane/EtOAc 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (1H, d×d, J=11.0, 8.3 Hz), 3.81 (1H, d×d, J=11.0, 4.4 Hz), 3.93 (1H, d×d, J=15.2, 4.7 Hz), 4.01 (1H, d×d, J=15.2, 6.4 Hz), 4.29–4.37 (1H, m), 4.77 (1H, d×d, J=5.2, 1.1 Hz), 5.58 (1H, d, J=5.2 Hz), 7.00–7.07 and 7.25–7.32 (3H and 2H, 2×m), 9.70 (1H, d, J=1.1 Hz). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 33.52, 46.62, 48.15, 64.82, 82.37, 115.51, 123.22, 129.94, 156.80, 165.52, 196.95. IR (ATR, cm^{-1}): $\nu_{NC=O}$=1760; $\nu_{HC=O}$=1730; ν_{max}=1596, 1496, 1400, 1226, 690. MS (70 eV) m/z (%): 390/2/4 (M^++1, 100).

3.5. Synthesis of (3*R*,4*S*)-1-(2,3-dibromo-2-methylpropyl)-4-hydroxymethyl-3-phenoxyazetidin-2-one 15

The synthesis of (3*R*,4*S*)-1-(2,3-dibromo-2-methylpropyl)-4-hydroxymethyl-3-phenoxyazetidin-2-one **15** was analogous to the synthesis of (3*R*,4*S*)-1-(2-bromo-2-propenyl)-4-hydroxymethyl-3-phenoxyazetidin-2-one **9a**, using (3*R*,4*R*)-4-formyl-1-(2-methyl-2-propenyl)-3-phenoxyazetidin-2-one **14** as the starting material. Compound **15** was obtained as a mixture of diastereomers (*dr* 84/16). The major isomer was isolated through column chromatography on silica gel.

*3.5.1. (3R,4S)-1-(2,3-Dibromo-2-methylpropyl)-4-hydroxymethyl-3-phenoxyazetidin-2-one **15**.* Spectral data of the major isomer. White crystals. Mp 87–88 °C. R_f=0.13 (hexane/EtOAc 4/1). Yield 58%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91 (3H, s), 2.16 (1H, d×d, *J*=8.9, 4.7 Hz), 3.55 (1H, d, *J*=15.1 Hz), 3.81 and 3.91 (2×1H, 2×d, *J*=10.5 Hz), 4.07–4.17 (2H, m), 4.18 (1H, d, *J*=15.1 Hz), 4.35–4.39 (1H, m), 5.38 (1H, d, *J*=5.0 Hz), 7.01–7.12 and 7.29–7.35 (3H and 2H, 2×m). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 28.99, 40.19, 50.36, 58.68, 59.95, 64.61, 80.99, 115.92, 123.09, 129.88, 157.15, 167.33. IR (ATR, cm^{-1}): ν_{OH}=3402; $\nu_{C=O}$=1728; ν_{max}=2926, 1494, 1365, 1224, 1050, 752, 692. MS (70 eV): *m*/*z* (%) 406/8/10 (M^++1, 100).

3.6. Synthesis of (3*R*,4*S*)-3-benzyloxy-1-(2,2,3-tribromopropyl)-4-hydroxymethylazetidin-2-one 16

To a solution of (3*R*,4*S*)-3-benzyloxy-1-(2-bromo-2-propenyl)-4-hydroxymethylazetidin-2-one **9c** (0.30 g, 0.92 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) was added a solution of Br_2 (0.15 g, 0.92 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL). After stirring at room temperature for 18 h, the solvent was evaporated and crude (3*R*,4*S*)-3-benzyloxy-1-(2,2,3-tribromopropyl)-4-hydroxymethylazetidin-2-one **16** was obtained, which was purified by column chromatography on silica gel to give the pure compound **16** in 82% yield.

*3.6.1. (3R,4S)-3-Benzyloxy-1-(2,2,3-tribromopropyl)-4-hydroxymethylazetidin-2-one **16**.* Yellow oil. Yield 82%. R_f=0.35 (hexane/EtOAc 3/2). $[\alpha]_D$ +57 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (1H, d, *J*=15.4 Hz), 3.93 (1H, d×d, *J*=13.2, 1.9 Hz), 4.04 (1H, d×d, *J*=13.2, 3.3 Hz), 4.15 (1H, d, *J*=11.8 Hz), 4.17 (1H, m), 4.21 (1H, d, *J*=11.8 Hz), 4.51 (1H, d, *J*=15.4 Hz), 4.71 (1H, d, *J*=11.6 Hz), 4.85 (1H, d, *J*=5.0 Hz), 4.96 (1H, d, *J*=11.6 Hz), 7.31–7.42 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.38, 53.41, 58.35, 59.62, 64.65, 73.68, 81.64, 128.24, 128.53, 128.73, 136.16, 168.54. IR (NaCl, cm^{-1}): ν_{OH}=3418; $\nu_{C=O}$=1759; ν_{max}=2925, 1394, 1158, 1047. MS (70 eV) *m*/*z* (%): 484/86/88/90 (M^++1, 100).

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