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Regio- and Diastereoselective Functionalization of 3-Amino-hexahydrooxazoninones

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Regio- and diastereoselective functionalization of 3-amino-hexahydrooxazoninones

B. Schurgers,^[a] J. Wouters,^[b] A. De Blicck,^[c] G. Van Lommen,^[c] C. Menet,^[c] and G. Verniest^[a]

Abstract: The regio- and diastereoselectivity of transformations of nine-membered lactams with a *Z*-double bond in the cyclic tether towards novel building blocks for medicinal chemistry was evaluated. To this end, 3-amino-hexahydrooxazoninones were synthesized using a standard ring closing metathesis (RCM) approach of easily available *O,N*-bisallylated serine derivatives. The obtained *Z*-double bond in the medium sized lactam was used as a handle to evaluate the stereoselectivity of electrophile induced transformations. It was shown that dibromination and electrophilic activation by NBS followed by attack of *O*-nucleophiles proceeded in a diastereoselective manner. Cyclization of obtained bromohydrins and face-selective epoxidation gave access to both diastereomers of the epoxidized lactams. Finally, a Heck-reaction of a bromobenzyl moiety at the lactam *N*-atom with the *Z*-double bond resulted in the diastereoselective formation of novel bicyclic bridged 9-membered lactams.

Introduction

The use of medium-sized ring structures, in particular nine-membered heterocycles, is not very widespread in medicinal chemistry. Although these types of substituted ring systems can offer additional value in terms of preferred conformational orientation of key substituents as well as in terms of creating novel IP space, the chemistry of nine-membered lactams is still underdeveloped.^{1,2} This is partly because of an often difficult synthesis due to entropically disfavoured ring closure reactions and the relatively high Prelog, Baeyer and Pitzer strain,³ and also because the limited amount of experimental data that demonstrate post-cyclization modifications of nine-membered ring systems.⁴ However, some examples of beautiful syntheses and selective transformations have shown the synthetic potential of such strained rings.⁵ As examples, azoninones bearing *E*-olefins have been synthesized via aza-Claisen rearrangements and display planar chirality which was used to transfer chirality in transannular reactions.⁶ Also nine-membered lactams with a *Z*-double bond have been synthesized⁷ and used in diastereoselective transannular cyclizations towards bicyclic amino acid derivatives.⁸ The often observed high stereoselectivity in functionalizations of nine-membered ring systems (including carbocycles or lactones) arises from the specific conformational preferences of the intermediate transition states, directed by both

steric and electronic factors.^{9,10} With respect to electrophilic additions to double bonds, reaction generally occurs at the most exposed face of the double bond as depicted in Figure 1.^{10b} For planar chiral *E*-nonenes as well as for *Z*-isomers, both diastereomeric reaction products are possible but highly selective transformations have been described as exemplified in Figure 1.¹⁰⁻¹² The difficulty in predicting the stereochemical outcome with nine-membered rings lies in the fact that subtle changes in the ring substituents can alter significantly the reactive conformation and hence reaction outcome.⁹ For instance, it has been shown that a change from a *N*-acyl to an *N*-benzoyl amide substituent changes the *cis-trans* geometry of the amide moiety in nine-membered lactams¹¹ and that diastereoselective dihydroxylation of substituted 3-propylcyclo-non-1-enes occurs at the opposite side (*cis* to the propyl, see Fig 1.) as initially assumed.¹² These examples highlight that, while the stereoselectivity of reactions with 8- and 10-membered rings can often be predicted in a reliable manner,¹³ this is less general for substituted nine-membered rings. Therefore, the experimental exploration of double bond transformations in unsaturated nine-membered amides can deliver new insights for the development of diastereoselective methods towards novel nine-membered ring compounds.

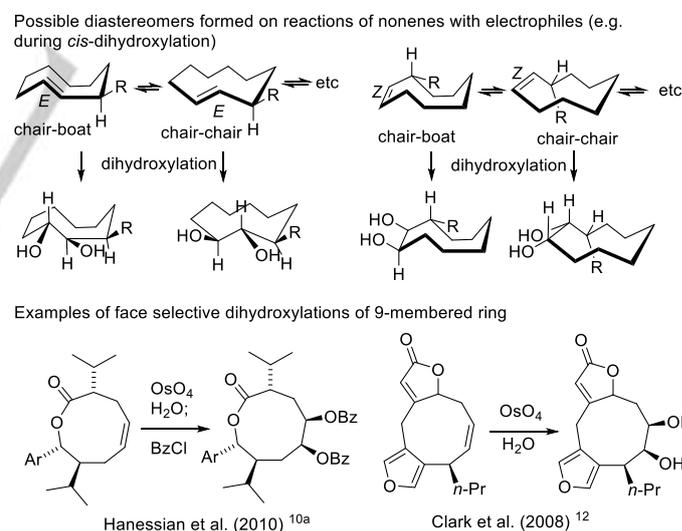


Figure 1. Selected examples of diastereoselective double bond transformations in unsaturated 9-membered rings.

Results and Discussion

For the preparation of novel 3-amino-oxaazoninones **3** (scheme 1) via RCM, α,ω -dienic amides **2** were synthesized by coupling of *O*-allylserines **1** with amines using (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo-

[a] Research group of Organic Chemistry, Department of Chemistry and Department of Bio-engineering Sciences, Faculty of Science and Bio-engineering Sciences, Vrije Universiteit Brussel (VUB), Pleinlaan 2, B-1050 Brussels, E-mail: gvernies@vub.be

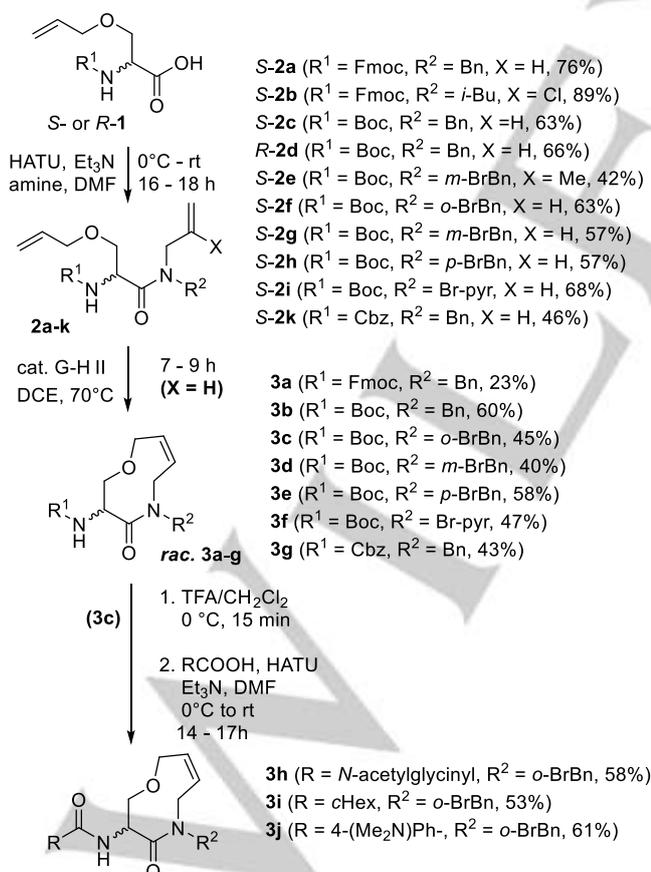
[b] Chemistry Department, Université de Namur, Rue de Bruxelles 61 - 5000 Namur, Belgium

[c] Department of Medicinal Chemistry, Galapagos NV, Generaal De Wittelaan L11-A3 B-2800 Mechelen, Belgium

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[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) as reported coupling agent.¹⁴ Optimal conditions included the treatment of the serine derivatives **1** with HATU and Et₃N in DMF at 0°C before adding amines. Next, the evaluation of the ring closing metathesis towards 9-membered lactams **3** using diene **2c** (Table 1) was performed. The use of 10 mol% of either Grubbs 2nd generation (GII) or Grubbs–Hoveyda 2nd generation (G-HII) catalyst in refluxing CH₂Cl₂ (entry 1 and 3) resulted in poor conversion or in the formation of side products when the reaction times were increased (entry 2 and 4). According to LCMS-analysis, the formation of oligomers and structural isomers of **2c** and **3b** was observed but these side products could not be isolated. Heating the reaction mixture to 70°C in 1,2-dichloroethane (entry 6) gave higher conversions, but still a considerable amount of oligomers was formed. Again, also at these temperatures, longer reaction times resulted in the formation of more side products (entry 7). To maximize the formation of **3b**, a limited reaction time combined with 2 subsequent additions of 5 mol% G-H II catalyst was required (entry 8). It should be noted that after the reaction was completed, a catalyst denaturated step was required to avoid metathesis side reactions during concentration and work-up. This was done by adding 10 equiv of Et₃N before extractive work-up and concentration. Attempts to lower the reaction temperature resulted in poor conversion (entry 9), or an increase in side products (entry 10).



Scheme 1. Synthesis of (*Z*)-3-aminohexahydrooxazinones **3a-j** via RCM.

Table 1. Evaluation of RCM of **2c** to **3b**

	Cat.	T	t (h)	Conv. (%) ^d	3b	2c isomer	3b isomer	Oligomers
1	GII ^a	Δ	7	47	49	4	22	25
2	GII ^a	Δ	18	51	44	23	19	14
3	G-HII ^a	Δ	8	18	51	-	-	49
4	G-HII ^a	Δ	16	62	53	4	5	38
5	G-HII ^b	Δ	4	95	42	5	4	49
6	G-HII ^a	70°C	5	83	56	2	3	39
7	G-HII ^a	70°C	17	100	41	7	5	47
8	G-HII^c	70°C	8	92	64	3	4	29
9	G-HII ^c	60°C	8	29	49	8	6	37
10	G-HII ^c	60°C	17	81	21	16	12	51

Reactions performed in dichloroethane (entries 6-10) or CH₂Cl₂ (for entries 1-5) at 2.10⁻³ mol L⁻¹, ^a10 mol%, ^b25 mol%, ^c2 x 5 mol%.^d percentages are given as area% based on UV response (HPLC) and are therefore not actual molar distributions but merely highlight the observed trends.

Applying the optimized RCM reaction conditions to diene precursors **2** gave rise to a collection of 9-membered rings **3a-g** in low to moderate yields over 7 – 9 h (Scheme 1). It should be noted that RCM did not work in our hands using dienes **2b** and **2e** where X = Cl or X = Me. Reactions at elevated temperatures in toluene (110°C) and/or using higher catalyst loadings only resulted in starting material and side products. Because of these results and the results obtained from earlier work on RCM towards related 7-membered lactams,¹⁴ it is suggested that the presence of a vinylic substituent in these types of substrates creates to much steric congestion for RCM to proceed. The *Z*-stereochemistry of the double bond was proven via X-ray analysis.¹⁵ Chiral derivatization of the resulting 9-membered rings followed by HPLC-MS analysis indicated that racemization occurred during RCM. *N*-Deprotection and coupling of the resulting free amine of **2c** to Marfey's reagent (1-fluoro-2,4-dinitrophenyl-5-L-alanine amide, FDAA)¹⁶ resulted in the corresponding diastereomer and giving one signal in HPLC, while a similar FDAA coupling to a mixture of **2c** and **2d** gave two separate signals. In contrast, after the ring closure, an analogous LC-MS analysis of the FDAA coupled **3b** showed the presence of two diastereomers and indicated that racemization occurred during RCM and not during synthesis of compounds **2**. The racemisation is the result from either the instability of the starting substrates, of the end product or the combination of both under the used conditions. Because attempts to decrease the reaction temperature unfortunately resulted in low conversions (Table 1, entries 9 and 10), no further studies were performed and following reactions using the lactams were performed on the racemic mixtures.

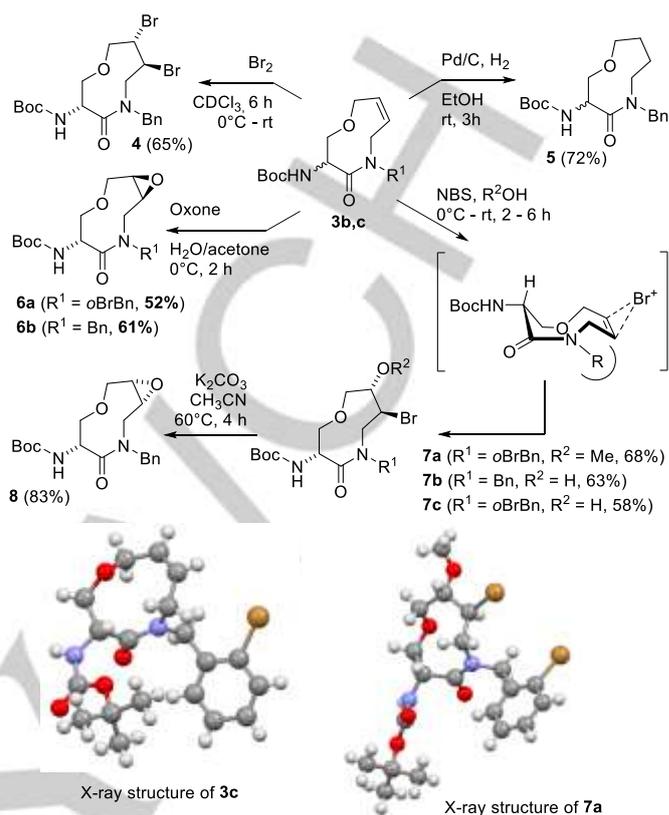
To demonstrate the potential use as building block for medicinal chemistry purposes, additional functionalisations of **3c** were performed using the 3-aminogroup as a handle. At first, TFA mediated *N*-Boc deprotection was followed by acylation of the resulting free amine to give 3-acylaminooxazinones in moderate to good yields via treatment with the corresponding acid in the presence of HATU. Next, functionalization of the double bond in oxazinones was explored to provide an extra

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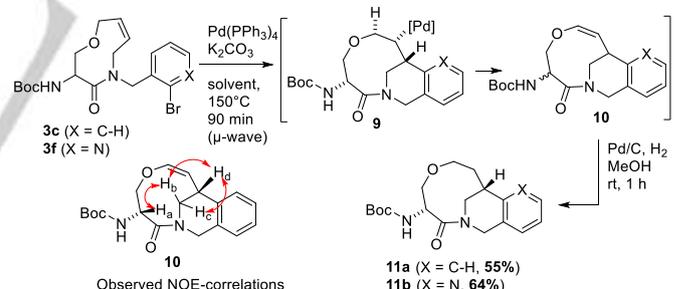
derivatisation handle. It should be noted that (diastereoselective) functionalisations of double bonds in nine-membered rings are not widespread and that extra experimental data can give further insight in the reactivity profile of such compounds. Treatment of oxazoninone **3c** with *N*-bromosuccinimide (NBS) in MeOH at 0°C and stirring at room temperature for two hours resulted in the formation of two isomers (ratio 4:1) of which only the major isomer was isolated by crystallization to give methoxybrominated nine-membered lactam **7a** in 68 % yield. X-Ray analysis of crystals unambiguously demonstrated the diastereoselectivity of the reaction.¹⁵ Apparently, the Boc-amino substituent forces the nine-membered ring in a conformation in which the initial bromonium complex is formed at opposite side of the Boc-amino substituent (possibly as chair-boat conformation as shown in Scheme 2) and where subsequent attack of the nucleophile occurs remotely from the *N*-Bn substituent. A related reaction using NBS in dioxane/H₂O resulted in bromohydrins **7b,c** in good yield. Again, good regio- and diastereoselectivity was obtained as the isolated products represented more than 80% of the reaction mixture as indicated by HPLC/MS. Also, a direct bromination of the double bond of **3b** using Br₂ yielded dibrominated compound **4** as a single diastereomer. To obtain both diastereomeric epoxides **6** and **8** (Scheme 2), direct epoxidation and ring closure from bromohydrins were evaluated. Whereas the reaction of **3b,c** with meta-chloroperbenzoic acid (mCPBA) in CH₂Cl₂ was low yielding, the treatment with Oxone® in a H₂O/acetone mixture at 0°C nicely gave rise to only one (racemic) diastereomer in good isolated yields. Prolonged reaction times resulted in the formation of the corresponding diols via attack of water. To prepare the other epoxide diastereomer, bromohydrin **7c** was treated with K₂CO₃ in CH₃CN at 60°C for 4 h. This resulted in a clean conversion to epoxide **8** in very good yield.

To provide an example of a saturated nine-membered analogue, the double bond was hydrogenated easily without removal of the benzyl protecting group.

In a next approach, an intramolecular Heck reaction was envisaged using bromoarylated structures **3c** and **3f** towards bridged oxazoninones. Treatment of **3c** with Pd(PPh₃)₄ in the presence of K₂CO₃ in DMF at 150°C (μ-wave) resulted in the clean formation of **10a** after 90 minutes. The position of the resulting double bond originates from the β-hydride elimination step, which can only occur with a proton next to the oxygen in the 9-membered ring due to the *cis*-requirement (see intermediate **9**). When applying similar reaction conditions on **3f** almost no reaction was observed. It was found that the use of dioxane greatly improved the reaction outcome, leading to the respective oxazoninones **10**. Because of possible stability problems of the enol ether, it was decided to not isolate and purify the formed compounds **10**, but reduce the double bond directly. Gratifyingly, treatment of **10** with H₂ in the presence of Pd on carbon cleanly transformed the enol ether into the saturated fused oxazoninones **11**. Cyclizations of this type are rare, but have been used before on related structures to synthesize the natural product cleavamine, which also contains a bridged nine-membered azaheterocycle core structure.¹⁷



Scheme 2. Diastereoselective double bond transformations of (*Z*)-3-aminohexahydrooxazinones **3**.



Scheme 3. Intramolecular Heck reactions of 3-aminohexahydrooxazinones **3**.

Conclusions

In conclusion it can be stated that a successful synthesis was developed towards 3-aminohexahydrooxazinones containing a *Z*-double bond using a standard ring closing metathesis (RCM) approach of easily available O,*N*-bisallylated serine derivatives. These compounds proved useful in electrophile induced transformations of the double bond showing high regio- and diastereoselectivity. Cyclization of obtained bromohydrins and face-selective epoxidation gave access to both diastereomers of the epoxidized lactams. Finally, a Heck-reaction of a bromobenzyl moiety at the lactam *N*-atom with the *Z*-double bond resulted in the diastereoselective formation of novel

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bicyclic bridged 9-membered heterocycles. Given the rising importance of medium-size ring compounds, the obtained scaffolds are not only of interest as building blocks for medicinal chemistry purposes, but the obtained insights are also of value to further map the reactivity of unsaturated nine-membered ring.

Experimental Section

Column chromatography purifications were conducted on silica gel 60 (40–63 μm ; Grace Davisil) or with a Grace Reveleris X2 Flash Chromatography System on silica gel (prepacked 40 μm ; Grace Reveleris) or C18 silica gel (prepacked 40 μm , Grace Reveleris). TLC was carried out on glass plates precoated with silica gel 60F254 (Merck); the spots were visualized under UV light ($\lambda = 254 \text{ nm}$) and/or KMnO_4 (aq.) was used as the revealing system. Preparative HPLC was conducted using a Gilson semi-preparative HPLC equipped with a Supelco Discovery Bio Wide Pore C18 column. Samples were analyzed on an Agilent 1100 Series HPLC equipped with a Supelco Discovery Bio Wide Pore C18 column (15 cm x 2.1 mm x 3 μm). The solvent system consists of 0.1% TFA in water and 0.1% TFA in acetonitrile. The samples were then eluted through the column using a gradient ranging from 3% acetonitrile to 97% acetonitrile over 20 minutes (standard gradient) at a flow rate of 0.3 mL min^{-1} . Melting points were acquired on a Buchi Melting Point B-540. IR absorption spectra were recorded on a Thermo Nicolet 700 FT-IR spectrophotometer. NMR measurements were performed on a Bruker Avance II spectrometer operating at ^1H and ^{13}C frequencies of 500 and 125 MHz. The sample temperature was set to 298 K. The deuterated solvent is mentioned in the analysis section and tetramethylsilane was used as an internal standard. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). High resolution mass spectrometry was conducted on a Waters Micromass QTOF in ES+ mode, using reserpine as the reference. Reactions using microwave irradiation were performed in a Biotage® Initiator+ microwave reactor (at 75W). X-ray diffraction data were collected at room temperature on a Gemini Ultra (Rigaku) diffractometer using Cu K α (1.54184 Å) radiation.

Synthesis of (Z)-3-aminohexahydrooxazinones 3

A representative procedure is given by the synthesis of **3c**. In a flame dried flask, *tert*-butyl 1-(allyl(2-bromobenzyl)amino)-3-(allyloxy)-1-oxopropan-2-ylcarbamate (1 equiv, 2.21 mmol, 1.0 g) was dissolved in commercially available dichloroethane (DCE; 2L; [2 mM] and degassed with N_2). To this solution was added the Grubbs-Hoveyda II catalyst (0.05 equiv, 0.11 mmol, 70 mg) and the reaction was heated to 85°C under inert atmosphere for 3 h. Another 0.05 equiv of catalyst was added and refluxing was continued for 4 h. The reaction mixture was allowed to cool to room temperature, after which triethylamine (0.5 equiv, 1.10 mmol) was added. This mixture was stirred for 16 h at room temperature and the solvent was removed under reduced pressure. The resulting crude mixture was purified by silica gel chromatography. Purification of the crude was done by silica gel chromatography using petroleum ether/EtOAc (9/1 to 6/1) to yield the title compound as a slightly brown oil, which solidified on standing, in 45% yield (422 mg); Mp: 126.3 – 127.8 °C; IR (ATR) 3423, 3318, 2978, 2927, 1707, 1629, 1438, 1162 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) $\delta = 1.47$ (s, 9H, 3 x CH_3), 3.37 – 3.53 (m, 2H, $\text{CH}_\alpha\text{-CH}_2\text{O}$ and $\text{CON-CH}_2\text{-CH=}$), 3.97 – 4.08 (m, 2H, $=\text{CH-CH}_2\text{-O}$ and $\text{CH}_\alpha\text{-CH}_2\text{O}$), 4.31 (d, $J = 15.8 \text{ Hz}$, 1H, $\text{CON-CH}_2\text{C}_{\text{arom}}$), 4.49 (dd, $J = 4.3$ and 15.5 Hz , 1H, $=\text{CH-CH}_2\text{O}$), 4.89 – 5.07 (m, 2H, CH_α and $\text{CONCH}_2\text{-CH=}$), 5.22 (d, $J = 15.8 \text{ Hz}$, 1H, $\text{CONCH}_2\text{C}_{\text{arom}}$), 5.75 – 5.94 (m, 3H, $\text{CH}=\text{CH}$ and OCONH), 7.13 – 7.33 (m, 3H, CH_{arom}), 7.56 (dd, $J = 1.0$ and 8.0 Hz , 1H, CH_{arom}) ppm; ^{13}C NMR (126 MHz, CDCl_3) $\delta = 28.3$ (3 x CH_3), 43.1 ($\text{CON-CH}_2\text{CH=}$), 48.2 ($\text{CONCH}_2\text{-C}_{\text{arom}}$), 51.9 (C_{α}), 69.5 ($=\text{CH-CH}_2\text{O}$), 73.1 ($\text{C}_{\alpha}\text{CH}_2\text{O}$), 79.8 (OCON), 123.8 ($\text{Br-C}_{\text{arom}}$), 126.7 ($\text{CH}_2\text{CH}=\text{CH}$), 127.8 (CH_{arom}), 129.0 (CH_{arom}), 129.2 (CH_{arom}), 132.2 ($\text{CH}_2\text{CH}=\text{CH}$), 132.9 (CH_{arom}), 135.6 (C_{arom}), 155.0 (OCON), 170.9 (CON) ppm; HRMS calcd for $[\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_4\text{Br} + \text{Na}]^+$: 447.0890 and 449.0872, found: 447.0885 and 449.0857.

Alkoxybromination of (Z)-3-aminohexahydrooxazinones 3.

A representative procedure is given for the synthesis of \pm -*tert*-butyl 7-bromo-5-(2-bromobenzyl)-8-methoxy-4-oxo-1,5-oxazanon-3-ylcarbamate **7a**. Compound **3c** (1 equiv, 0.282 mmol, 120 mg) was dissolved in MeOH

(3.0 mL [94 mM]) at 0°C. NBS (1 equiv, 0.28 mmol, 50 mg) was added and the ice bath was removed. After stirring for 2 h a white suspension was formed and the liquid was yellow. CH_2Cl_2 (20 mL) was added (the suspension dissolved) and H_2O (20 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO_4 , filtered and evaporated to a residue. The crude residue was dissolved in a mixture of hot EtOAc and Et $_2\text{O}$ and was allowed to crystallize to yield the title compound as white crystals in 68 % yield (103 mg) after two crystallization rounds. Mp: 185 – 187 °C (decomp.); IR (ATR): 3336, 2966, 2930, 2882, 1683, 1629, 1524, 1091 and 753 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) $\delta = 1.45$ (s, 9 H, 3 x CH_3), 3.45 (s, 3H, OCH_3), 3.50 – 3.57 (m, 2H, $\text{N-CH}_2\text{CHBr}$ and CH_2OCH_3), 3.60 (t, $J = 10.7 \text{ Hz}$, 1H, $\text{CH}_\alpha\text{CH}_2\text{O}$), 3.86 (dd, $J = 1.1$ and 12.8 Hz , 1H, OCH_2CHOMe), 3.95 (dd, $J = 1.8$ and 10.7 Hz , 1H, $\text{CH}_\alpha\text{CH}_2\text{O}$), 4.21 (dd, $J = 1.1$ and 12.8 Hz , 1H, OCH_2CHOMe), 4.29 (d, $J = 15.9 \text{ Hz}$, 1H, $\text{NCH}_2\text{-C}_{\text{arom}}$), 4.41 – 4.47 (m, 1H, CHBr), 4.77 (dd, $J = 5.0$ and 15.5 Hz , 1H, NCH_2CH), 4.80 – 4.89 (m, 1H, CH_α), 5.36 (d, $J = 15.9 \text{ Hz}$, 1H, $\text{NCH}_2\text{C}_{\text{arom}}$), 5.69 (d, $J = 7.1 \text{ Hz}$, 1H, OCONH), 7.13 – 7.33 (m, 3H, CH_{arom}), 7.58 (d, $J = 8.0 \text{ Hz}$, 2H, CH_{arom}) ppm; ^{13}C NMR (126 MHz, CDCl_3) $\delta = 28.6$ (3x CH_3), 47.6 (CHBr), 48.6 ($\text{NCH}_2\text{C}_{\text{arom}}$), 51.4 (NCH_2CHBr and CH_α), 58.7 (OCH_3), 68.3 ($\text{OCH}_2\text{CH}_2\text{OCH}_3$), 72.8 ($\text{CH}_\alpha\text{CH}_2\text{O}$), 80.1 ($(\text{CH}_3)_3\text{CO}$), 84.8 (CH_2OCH_3), 124.0 ($\text{Br-C}_{\text{arom}}$), 128.1 (CH_{arom}), 129.2 (CH_{arom}), 129.4 (CH_{arom}), 133.2 (CH_{arom}), 135.3 (C_{arom}), 155.2 (OCON), 171.5 (CON) ppm; HRMS calcd for $[\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5\text{Br}_2 + \text{H}]^+$: 535.0438 and 537.0419 and 539.0402, found: 535.0449 and 537.0437 and 539.0430.

Synthesis of bridged compounds 11.

A representative procedure is given for the synthesis of *tert*-butyl [10-oxo-13-oxa-9-azatricyclo[7.6.1.0 2,7]hexadeca-2,4,6-trien-11-yl]carbamate **11a**. In a microwave vial, bromide **3c** (1 equiv, 0.364 mmol, 150 mg) was dissolved in a suspension of K_2CO_3 (2.5 equiv, 0.911 mmol, 120 mg) in degassed (N_2) DMF (20 mL, [0.01 M]), Pd(PPh_3) $_4$ (0.05 equiv, 0.018 mmol, 20 mg) was added and the vial was sealed under an N_2 atmosphere. The reaction mixture was heated in a microwave reactor for 60 minutes at 120°C (75W). The solvent was evaporated under reduced pressure and the resulting crude was purified by silica gel chromatography using 12% EtOAc in petroleum ether to give **10a** in 60% yield as a slightly brown oil which solidified upon standing. The obtained **10a** (1 equiv., 0.382 mmol, 145 mg) was dissolved in MeOH (4 mL, [0.1 M]). Palladium on carbon (0.1 equiv, 0.038 mmol, 50 mg) was added and the reaction mixture was brought under 1 atm H_2 (balloon). After stirring for 7 h at room temperature, CH_2Cl_2 (3 mL) was added and the mixture was filtered over a plug of silica gel using 20 mL of CH_2Cl_2 . The filtrate was evaporated to yield the title compound as a transparent oil in 90% yield (126 mg). IR (ATR) 3426, 2944, 1712, 1648, 1416, 1350 and 1156 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) $\delta = 1.47$ (s, 9H, 3 x CH_3), 1.46 – 1.57 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}$), 1.82 – 1.90 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}$), 3.03 (d(br), $J = 10.0 \text{ Hz}$, 1H, $\text{NCH}_2\text{CHC}_{\text{arom}}$), 3.37 (t, $J = 13.8 \text{ Hz}$, 1H, $\text{CH}_\alpha\text{CH}_2\text{O}$), 3.40 (d, $J = 12.5 \text{ Hz}$, 1H, NCH_2CH), 3.59 (d(br), $J = 15.1 \text{ Hz}$, 1H, OCH_2CH_2), 3.96 (d, $J = 15.1 \text{ Hz}$, 1H, OCH_2CH_2), 3.97 (d, $J = 10.0 \text{ Hz}$, 1H, NCH_2CH), 3.99 (d, $J = 13.8 \text{ Hz}$, 1H, $\text{CH}_\alpha\text{CH}_2\text{O}$), 4.22 (d, $J = 17.5 \text{ Hz}$, 1H, $\text{NCH}_2\text{C}_{\text{arom}}$), 4.75 (t, $J = 3.8 \text{ Hz}$, 1H, CH_α), 5.04 (d, $J = 12.5 \text{ Hz}$, 1H, NCH_2CH), 5.58 (d, $J = 17.5 \text{ Hz}$, 1H, $\text{NCH}_2\text{C}_{\text{arom}}$), 5.89 (d, $J = 5.0 \text{ Hz}$, 1H, NH), 7.10 – 7.23 (m, 4H, CH_{arom}) ppm; ^{13}C NMR (126 MHz, CDCl_3) $\delta = 28.6$ (3 x CH_3), 32.7 ($\text{CH}_2\text{CH}_2\text{CH}$), 39.7 ($\text{CH}_2\text{CH}_2\text{CH}$), 45.2 ($\text{NCH}_2\text{C}_{\text{arom}}$), 46.3 (NCH_2CH), 53.2 (CH_α), 70.4 (OCH_2CH_2), 71.0 ($\text{CH}_\alpha\text{CH}_2\text{O}$), 79.9 ($(\text{CH}_3)_3\text{C}$), 126.8 (CH_{arom}), 126.6 (CH_{arom}), 127.1 (CH_{arom}), 128.5 (CH_{arom}), 132.4 (C_{arom}), 139.4 (C_{arom}), 155.2 (OCON), 170.6 (CON) ppm; HRMS calcd for $[\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4 - \text{Boc} + \text{H}]^+$: 247.1441, found: 247.1429, calcd for $[\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4 + \text{Na}]^+$: 369.1785, found 369.1783.

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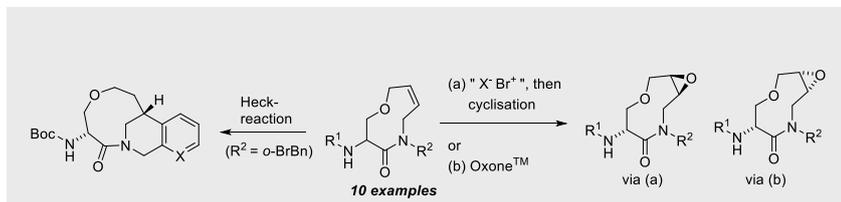
Keywords: Medium-ring compounds; Heck reaction; Metathesis; Cyclization; Diastereoselectivity.

- [1] J.-K. Jung, N.-S. Choi and Y.-G. Suh, *Arch. Pharm. Res.* **2004**, *27*, 985-989.
- [2] Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125-196.
- [3] (a) Prelog, V. *J. Chem. Soc.* **1950**, 420-428; (b) For a review on the effect of ring strain in cyclisations, see C. Galli, L. Mandolini, *Eur. J. Org. Chem.* **2000**, *188*, 3117-3125.
- [4] P. A. Evans, A. B. Holmes, *Tetrahedron* **1991**, *47*, 9131-9166.
- [5] (a) D. O. Tymoshenko, in: *Comprehensive Heterocyclic Chemistry III*, Vol 14, 2008, 547-611; (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3007; (c) For a review on medium-sized ring ethers, see: A. S. Kleinke, D. Webb, T. F. Jamison, *Tetrahedron* **2012**, *68*, 6999-7018.
- [6] A. Sudau, W. Münch, U. Nubbemeyer, J. W. Bats, *J. Org. Chem.* **2000**, *65*, 1710-1720 and cited references..
- [7] (a) L. Banfi, A. Basso, G. Guanti, R. Riva, *Tetrahedron Lett.* **2003**, *44*, 7655-7658. (b) S. A. Dietrich, L. Banfi, A. Basso, G. Damonte, G. Guanti, R. Riva, *Org. Biomol. Chem.* **2005**, *3*, 97-106; (c) R. Kaul, S. Surprenant, W. D. Lubell, *J. Org. Chem.* **2005**, *70*, 3838-3844.
- [8] (a) S. Surprenant, W. Lubell, *Org. Lett.* **2006**, *8*, 2851. (b) N. D. P. Atmuri, W. D. Lubell, *J. Org. Chem.* **2015**, *80*, 4904.
- [9] (a) W. C. Still, I. Galynker, *Tetrahedron* **1981**, *37*, 3981-3996; For a discussion on nine-membered ring conformations, see (b) D. G. Evans, J. C. A. Boeyens, *Acta Cryst.* **1990**, *B46*, 524-532; (c) E. W. Warnhoff, V. Srinivasan, *Can. J. Chem.* **1973**, *51*, 3955; (d) I. Yavari, H. Kabiri-Fard, S. Moradi, *J. Chem. Res.* **2000**, 384-385; (e) D. M. Pawar, S. D. Miggins, S. V. Smith, E. A. Noe, *J. Org. Chem.* **1999**, *64*, 2418 and references cited therein.
- [10] For stereoselective transformations of nine-membered rings, see e.g. (a) S. Hanessian, S. Guesné, E. Chénard, *Org. Lett.* **2010**, *12*, 1816-1819; (b) E. Vedejs, D. M. Gapinski, *J. Am. Chem. Soc.* **1983**, *105*, 5058; (c) B. E. Maryanoff, M. Parvez, R. A. Olofson, *J. Org. Chem.* **1990**, *55*, 760; (d) S. S. Rankin, J. J. Caldwell, N. B. Cronin, R. L. M. van Montfort, I. Collins, *Eur. J. Org. Chem.* **2016**, 4496-4507.
- [11] S. Yamada, A. Homma, *Chem. Commun.* **2002**, *22*, 2656-2657.
- [12] J. S. Clark, J. M. Northall, F. Marlin, B. Nay, C. Wilson, A. J. Blake, M. J. Waring, *Org. Biomol. Chem.* **2008**, *6*, 4012.
- [13] (a) Still, C. W. *J. Am. Chem. Soc.* **1979**, *101*, 2493-2495; (b) Schreiber, S.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971-5974; (c) Vedejs, E.; Dent III, W. H.; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437.
- [14] Schurgers, B.; Brigou, B.; Urbanczyk-Lipkowska, Z.; Tourwé, D.; Ballet, S.; De Profit, F.; Van Lommen, G.; Verniest, G. *Org. Lett.* **2014**, *16*, 3712.
- [15] See Supporting Information file for structural X-ray analysis.
- [16] Bhushan, R.; Brückner, H. *J. Chromatogr. B* **2011**, *879*, 3148-3161.
- [17] Bannasar, M.-L.; Solé, D.; Zulaica, E.; Alonso, S. *Org. Lett.* **2011**, *13*, 2042-2045.

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Entry for the Table of Contents

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Nine-membered 3-aminohexahydrooxazinones containing a *Z*-double bond in the cyclic tether were prepared via RCM and subjected to electrophile induced transformations, giving rise to diastereoselective bromination, alkoxybromination and epoxidation. These results can give new insights into the influence of nine-membered ring conformation on reaction selectivity.

*one or two words that highlight the emphasis of the paper or the field of the study

Key Topic* Diastereoselective transformations of nine-membered heterocycles

*B. Schurgers, J. Wouters, A. De Blicke, G. Van Lommen, C. Menet, G. Verniest**

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Regio- and diastereoselective functionalization of 3-amino-hexahydrooxazinones